

PATENT COOPERATION TREATY

14

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-12420	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/16319	International filing date (day/month/year) 11/07/2000	Priority date (day/month/year) 19/07/1999
International Patent Classification (IPC) or national classification and IPC C07D209/22		
Applicant ELI LILLY AND COMPANY et al		



1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 136 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand [19/01/2001] 24.01.01	Date of completion of this report 28.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Feiler, L Telephone No. +49 89 2399 8282 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/16319

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*):

Description, pages:

1-109 as received on 13/06/2001 with letter of 11/06/2001

Claims, No.:

1-26 as received on 13/06/2001 with letter of 11/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-18, 21-26.

because:

- ☒ the said international application, or the said claims Nos. 22, 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-18, 21, 24-26.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19, 20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	19, 20
Industrial applicability (IA)	Yes:	Claims	19, 20

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No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/16319

1. With letter of 11/06/01 the Applicant has filed a "replacement application comprising description pages 1-109 and Claims 1-26. It would appear that these documents do not indicate the amendments indicated in the response to the written opinion dated 16/03/0; they are essentially identical to the document originally filed.

2. Claims 22 and 23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

It has to be stressed that subject matter of Claims 1-18 has not been searched completely. Consequently, the following observations apply to **subject matter of Claim 19** and dependent claims only.

3. Cited Documents

EP-A-0675110= D1

EP-A-0620215= D2

US-A-5684034= D3

WO-A-0037358= D4

WO-A-9921559= D5

WO-A-9921546= D6

EP-A-0952149= D7

WO-A-9637469= D8

WO-A-9106537= D9

J. Med. Chem. 39(1996), pp. 5119-5139= D10

The indicated designation will be used throughout the examination procedure.

D4 and D7 are P-documents.

4. Novelty

The subject-matter of Claim 19 differs from D1 essentially due to the fact that the 4-position of the indole moiety is substituted by an acidic group (e.g. -COOH) whereas the corresponding position of the compounds of Claim 19 of the application comprises a carbamoyl group.

D2, D3 and D6 disclose indole-3-acetamid derivatives whereas the compounds of Claim 19 of the application are indole-3-glyoxylamides.

According to D4 the 3-indole substituent is an oxime amide or oxime thioamide. D5 refers to a specific indol-4-yloxyacetic morpholino-N-ethylester.

D7 discloses carbazole derivatives, D8 refers to N-benzylindol-3-yl propanoic acid, D10 discloses indole-3-acetamides and D9 comprises indole derivatives not considered according to the application.

The subject-matter claimed can therefore be considered novel.

5. Inventive Step - Breadth of Claims

5.1 Subjective Problem

According to the application (p. 1, first paragraph and page 2, lines 14-16) the problem underlying the invention is to be seen in the provision of further compounds which are inhibitors of mammalian secretory phospholipase A₂ (sPLA₂) and are therefore useful to treat inflammatory diseases.

5.2 Relevant and closest prior art

Documents D1-D3, D5, D6, D9 and D10 are considered to be relevant for the assessment of inventive step since these compounds come structurally close to those comprised by Claim 19 of the application and also have the same qualitative activity. If the claimed priority date is not valid D4 may also come into picture.

The closest prior art is given by D1.

5.3 Objectively solved problem

The application documents disclose the test methodology and quantitative test data according to the table of page 109 so that it can be said that at least the tested compounds solve the problem defined above.

5.4 Evaluation of the solution of the problem

D1-D3, D5, D6, D9 and D10 disclose compounds structurally very similar to those of the present application.

The products of those documents also solve the problem of providing compounds which inhibit mamalian sPLA₂.

The person skilled in the art seeking a solution to the problem defined above would therefore have been prompted to consider further derivatives of compounds which are already known to solve the above defined problem. In this context it is to be stressed that e.g. D1 discloses that the R⁴ corresponding substituent is an acidic group e.g. the -COOH group, but D5 and D6 disclose that this group can be derivatisised (ester functions) without changing the qualitative activity. In other words the compounds of D5

and D6 could be considered as prodrugs of D1-compounds. Consequently, the compounds of the invention being amide derivatives are to be considered as further prodrugs of D1-compounds.

The person skilled in the art would have been able to infer that a modification of the proposed type would have no effect on the activity profile so that he would have considered the proposed solution in the expectation of success.

The solution of the technical problem defined in point 5.1 according to the application is therefore obvious in the light of the prior art and thus the subject-matter of the present Claim 19 cannot be considered to be inventive.

6. Industrial applicability

For the assessment of the present claims 22 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7. Clarity

- In Claim 19 (L_4) remains undefined
- Claim 20 appears twice; specific compounds are claimed in the second Claim 20 already claimed in the first one; this is considered to be superfluous and should be avoided.
- Claim 24 is unclear.

8. Suggestions

In a possible national or regional examination procedure an inventive step could possibly be acknowledged should comparative data be submitted which show that apart from the technical problem defined in point 4.1 another, e.g. more exacting, problem, which can be derived from the application as originally filed (e.g. surprising improvement), existed and has actually been solved by originally disclosed technical

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features, which would need to be incorporated in Claim 19.

In this respect it should be borne in mind that the compounds of the closest prior D1 must bear the closest possible structural resemblance in order that the comparison be valid. A suitable comparison would be e.g.:

Examples 1 and 17 of D1 versus corresponding compounds of the application whereby all possible variations should be included.

The breadth of the claims should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based.

Even if it turns out that the tested compounds of page 109 solve the problem defined in point 8, first paragraph the proposed broadness goes far beyond of what could be considered to be a reasonable generalisation:

L_4 is always $-OCH_2-$;

R_b is the residue of simple amino acids only;

$(R_{13})_t$ is always H;

R_{16} is H and

R^{22} is an alkyl only.

It is not reasonable e.g. to define NR_b as "an amino acid residue of a natural or unnatural amino acid" or to define L_4 (which was obviously intended to mean (Lc)) other than $-OCH_2-$.

The description should be adapted to new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

All the documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.

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Novel sPLA₂ InhibitorsField of the Invention

This invention relates to novel indole compounds
5 useful for Inflammatory Diseases.

Background of the Invention

The structure and physical properties of human non-
pancreatic secretory phospholipase A₂ (hereinafter
10 called, "sPLA₂") has been thoroughly described in two
articles, namely, "Cloning and Recombinant Expression of
Phospholipase A₂ Present in Rheumatoid Arthritic
Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski,
Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.;
15 Kloss, Jean; and Johnson, Lorin K.; The Journal of
Biological Chemistry, Vol. 264, No. 10, Issue of April
5, pp. 5335-5338, 1989; and "Structure and Properties of
a Human Non-pancreatic Phospholipase A₂" by Kramer, Ruth
M.; Hession, Catherine; Johansen, Berit; Hayes,
20 Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard,
Richard; and Pepinsky, R. Blake; The Journal of
Biological Chemistry, Vol. 264, No. 10, Issue of April
5, pp. 5768-5775, 1989; the disclosures of which are
incorporated herein by reference.

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It is believed that sPLA₂ is a rate limiting nzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA₂ mediated release
5 of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA₂; such as sepsis or rheumatoid arthritis.

10 It is desirable to develop new compounds and treatments for sPLA₂ induced diseases.

Summary of the Invention

This invention provides novel indole compounds
15 having potent and selective effectiveness as inhibitors of mammalian sPLA₂.

This invention is also the use of novel indole compounds useful in the treatment and prevention of
20 Inflammatory Diseases.

This invention is also the use of novel of indole compounds to inhibit mammalian sPLA₂ mediated release of fatty acids.

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This invention is also a pharmaceutical composition containing any of the indole compounds of the invention.

5 **I. Definitions:**

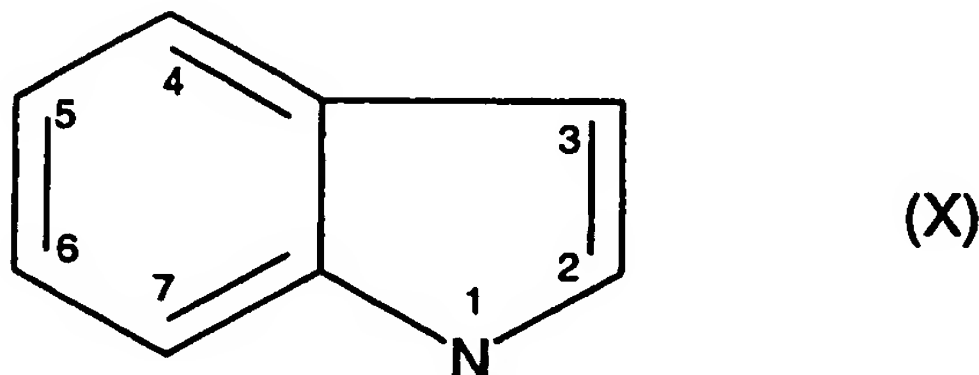
 The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, 10 allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, 15 enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, 20 arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, 25 bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing),

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miscellaneous forms of arthritis, neuropathic joint
disease (charco and joint), hemarthrosis (hemarthrosic),
Henoch-Schonlein Purpura, hypertrophic osteoarthropathy,
multicentric reticulohistiocytosis, arthritis associated
5 with certain diseases, surcoilosis, hemochromatosis,
sickle cell disease and other hemoglobinopathries,
hyperlipoproteineimia, hypogammaglobulinemia,
hyperparathyroidism, acromegaly, familial Mediterranean
fever, Behat's Disease, systemic lupus erythrematosis,
10 or relapsing polychondritis and related diseases which
comprises administering to a mammal in need of such
treatment a therapeutically effective amount of the
compound of formula I in an amount sufficient to inhibit
SPLA2 mediated release of fatty acid and to thereby
15 inhibit or prevent the arachidonic acid cascade and its
deleterious products.

The term, "indole nucleus" refers to a nucleus
(having numbered positions) with the structural
20 formula (X):



The indole compounds of the invention employ
certain defining terms as follows:

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The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary
5 butyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated
10 number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group
15 containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or
20 unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodinyll, piperidinyll, furanyl,
25 thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl,

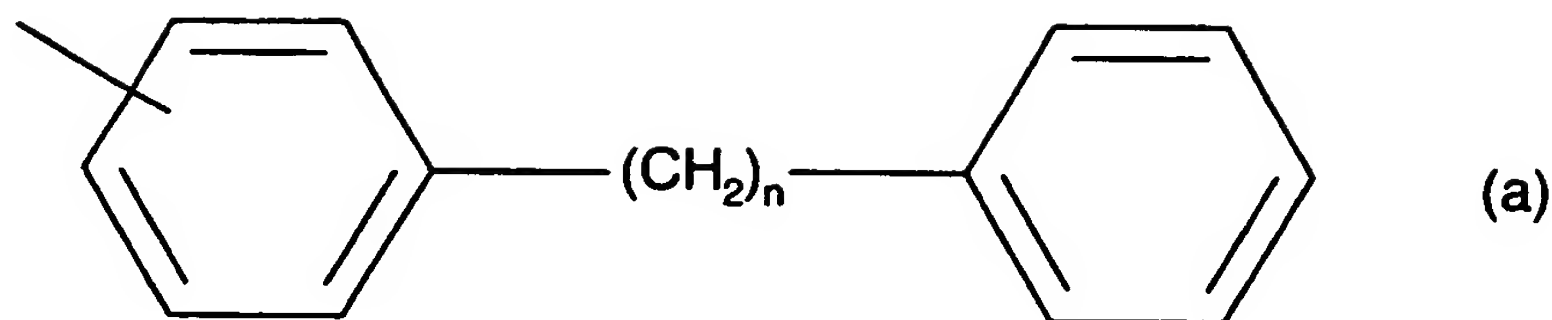
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indolyl, carbazolyl, norharmanyl, azaindolyl,
benzofuranyl, dibenzofuranyl, dibenzothiophenyl,
indazolyl, imidazo(1.2-A)pyridinyl, benzotriazolyl,
anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl,
5 benzothiazolyl, purinyl, pyridinyl, dipyridyl,
phenylpyridinyl, benzylpyridinyl, pyrimidinyl,
phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,
phthalazinyl, quinazolinyl, morpholino, thiomorpholino,
homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl,
10 oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-
dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny,
hexamethyleneiminium, heptamethyleneiminium, piperazinyl
and quinoxalinyl.

15

The term, "carbocyclic radical" refers to radicals
derived from a saturated or unsaturated, substituted or
unsubstituted 5 to 14 membered organic nucleus whose ring
forming atoms (other than hydrogen) are solely carbon
20 atoms. Typical carbocyclic radicals are cycloalkyl,
cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl,
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
indenyl, stilbenyl, terphenyl, diphenylethylenyl,
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
25 biphenyl, bibenzyl and related bibenzyl homologues
represented by the formula (a):

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where n is a number from 1 to 8.

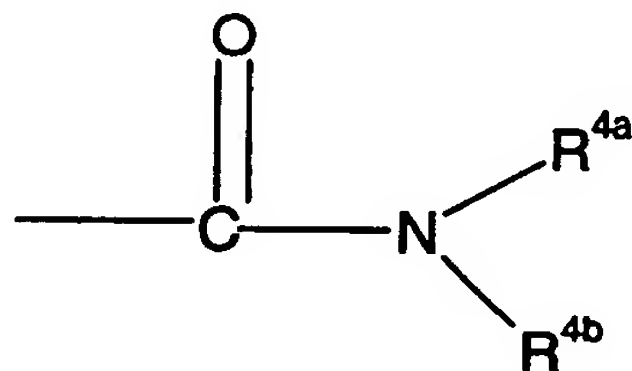
5 The term, "non-interfering substituent", refers to
radicals suitable for substitution at positions 4,5,6
and/or 7 of the indole nucleus and on other nucleus
substituents (as hereinafter described for Formula I),
and radicals suitable for substitution on the
10 heterocyclic radical and carbocyclic radical as defined
above. Illustrative non-interfering radicals are C₁-C₈
alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl,
C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl,
phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈
15 alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂
alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂
alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂
alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio,
C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈
20 alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈
haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl,
-C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy,
phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino,

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bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$,
chloro, cyano, cyanoguanidiny, fluoro, guanidino,
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,
iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl,
5 and carbonyl; where n is from 1 to 8 and R is C_1-C_8
alkyl.

The term, "organic substituent" refers to a
monovalent radical consisting of carbon and hydrogen
10 with or without oxygen, nitrogen, sulfur, halogen, or
other elements. Illustrative organic substituents are
 C_1-C_8 alkyl, aryl, C_7-C_{14} aralkyl, C_7-C_{14} alkaryl, C_3-C_8
cycloalkyl, C_1-C_8 alkoxyalkyl and these groups
substitued with halogen, $-CF_3$, $-OH$, C_1-C_8 alkyl, amino,
15 carbonyl, and $-CN$.

The term, "acylamino acid group" is represented by
the formula:



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wherein R^{4a} is selected from the group consisting of H,
 (C_1-C_6) alkyl, (C_1-C_6) alkoxy, heteroaryl and aryl, $-CF_3$;
and wherein NR^{4b} is an amino acid residue with the

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nitrogen atom being part of the amino group of the amino acid. A typical amino acid is selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine, asparagine, cysteine, glutamine, glutamic acid, histidine, lysine, methionine, serine, threonine, tryptophan, tyrosine and derivatives thereof. Also contemplated within the definition of amino acid is *l*-proline, *d*-proline and derivatives thereof. Also contemplated within the definition of amino acids are peptides, polypeptides and derivatives thereof.

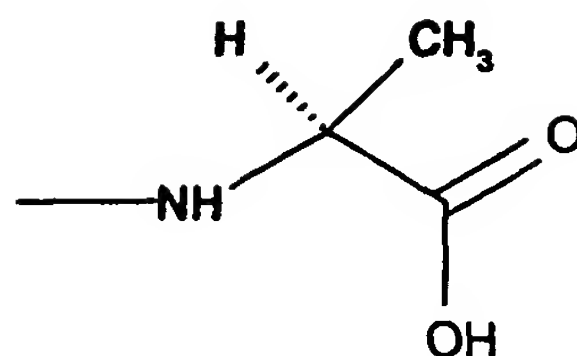
The term "substituted group" is an organic group substituted with one or more non-interfering substituents.

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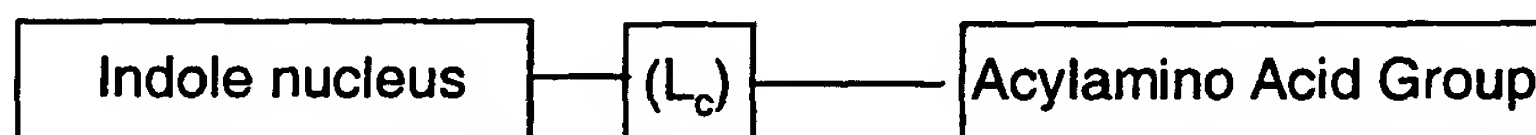
The terms, "amino acid residue" refer to the portion of the amino acid group coupled at the nitrogen atom of the amino terminus. It is the amino acid less a hydrogen atom from the amino terminus. It is further illustrated as used herein for the amino acid alanine attached at the nitrogen atom as shown below:

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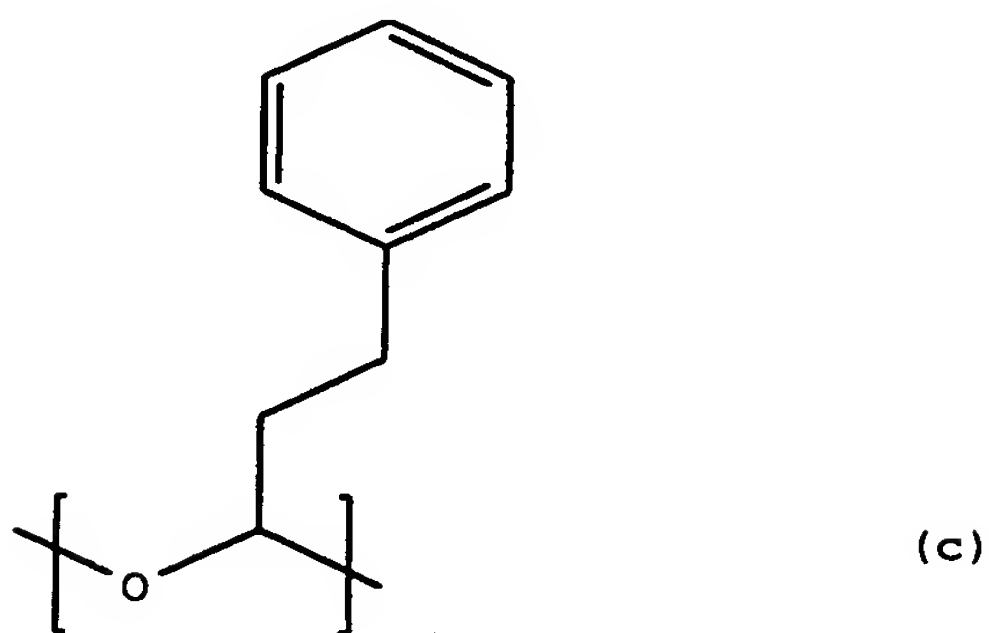
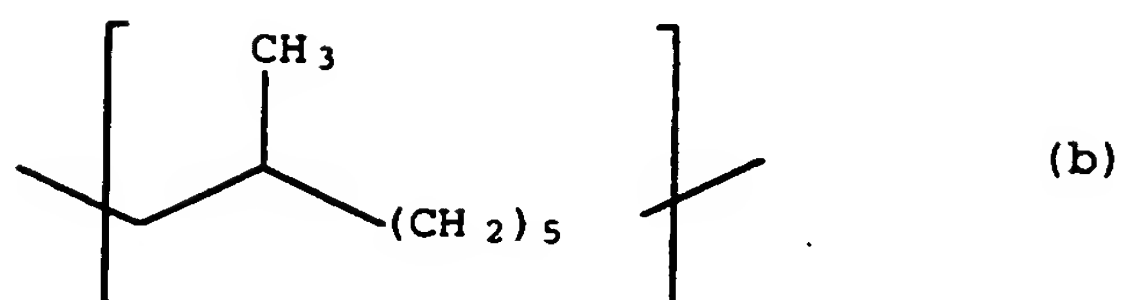
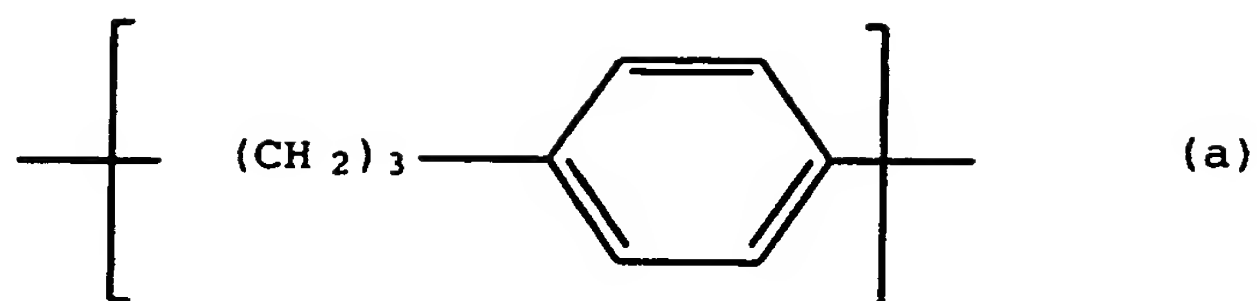


The words, "acylamino acid linker" refer to a divalent linking group symbolized as, $-(L_C)-$, which has the function of joining the 4 - position of the indole nucleus to an acylamino acid group in the general relationship:



The words, "acylamino acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group $-(L_C)-$ that connects the 4 - position of the indole nucleus with the acylamino acid group. The presence of a carbocyclic ring in $-(L_C)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_C)-$. Illustrative acylamino acid linker groups are;

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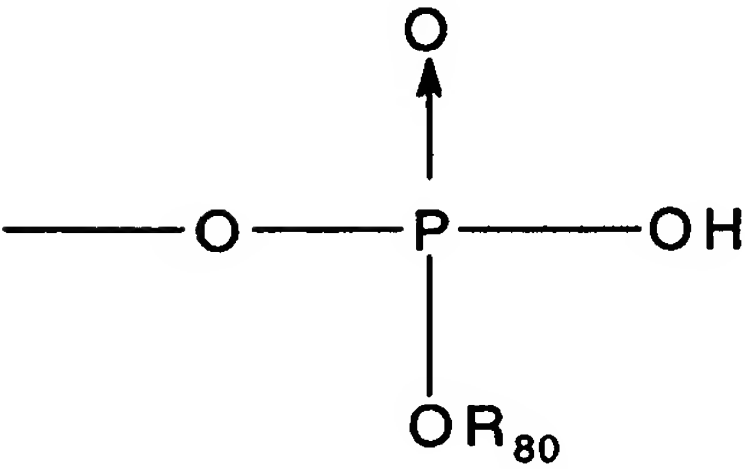
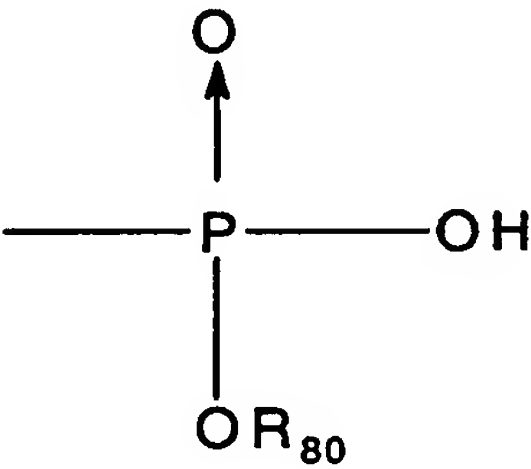
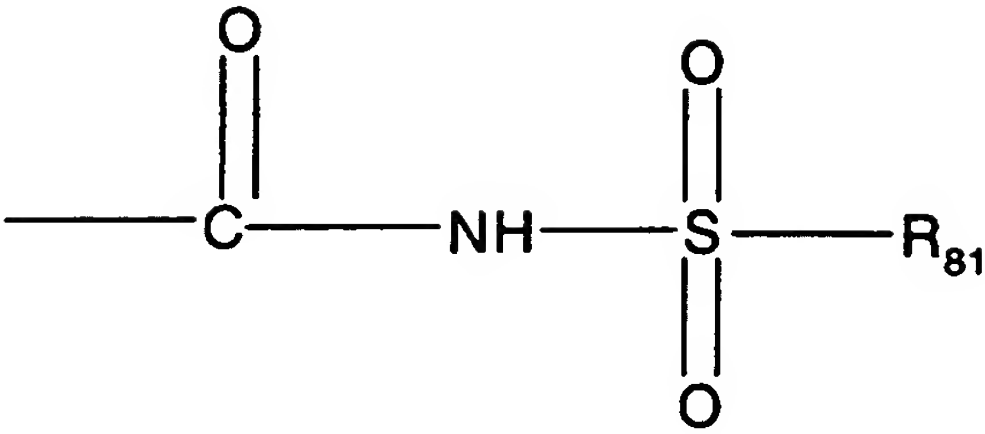
wherein, groups (a), (b) and (c) have acid linker lengths of 5, 7, and 2, respectively.

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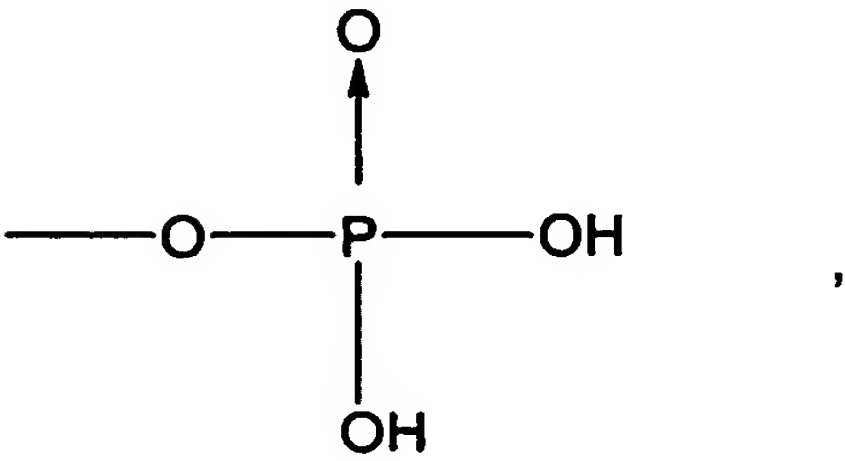
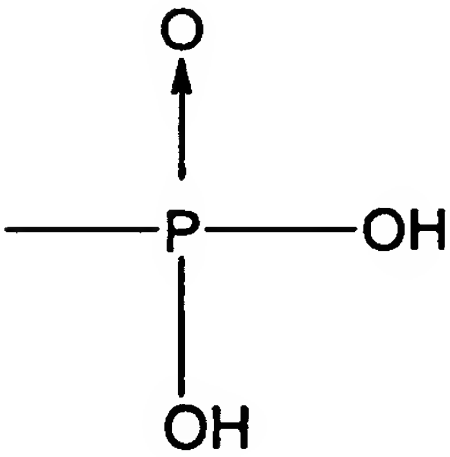
The term, "(acidic group)" means an organic group which when attached to an indole nucleus at position 5, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

-5-tetrazolyl,

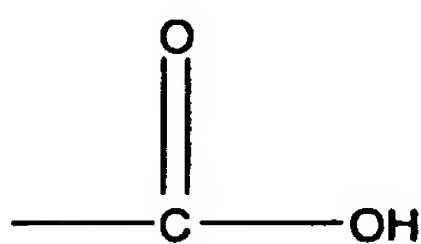
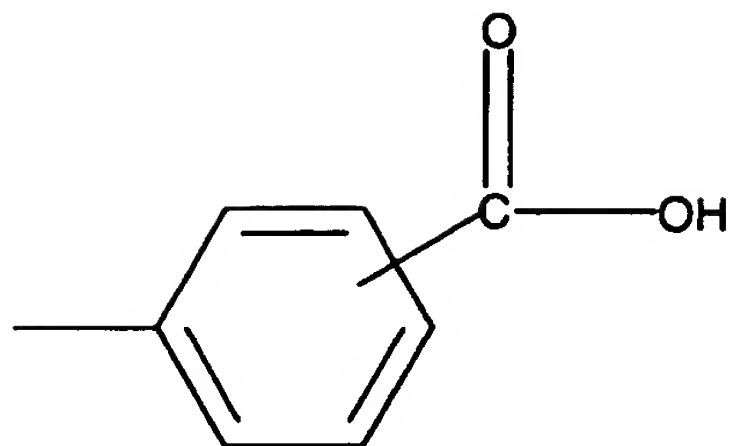
-SO₃H,



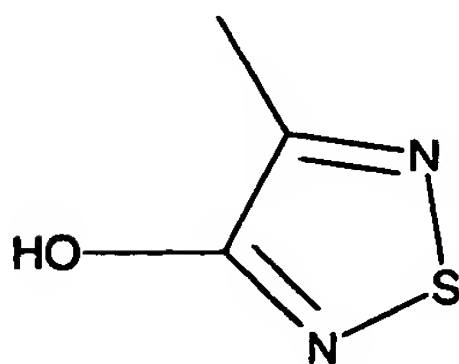
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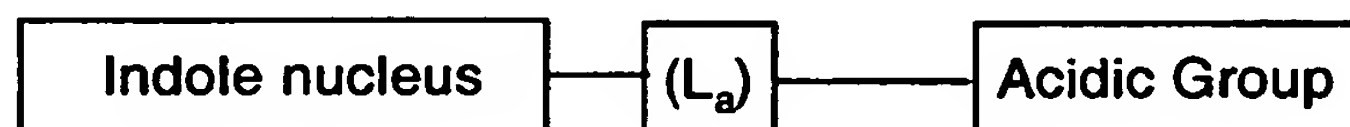


or



where n is 1 to 8, R_{g0} is a metal or C₁-C₈ and R_{g1}
5 is an organic substituent or -CF₃.

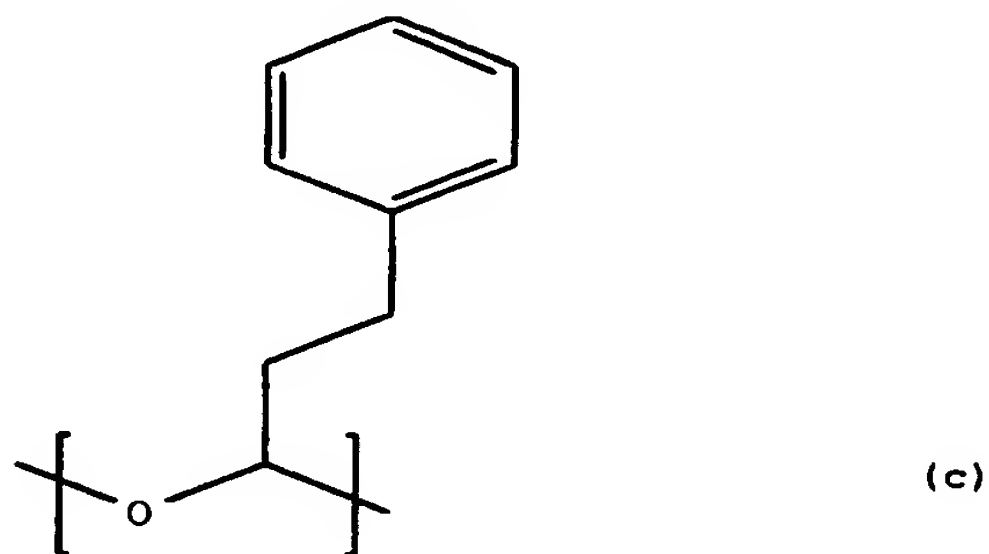
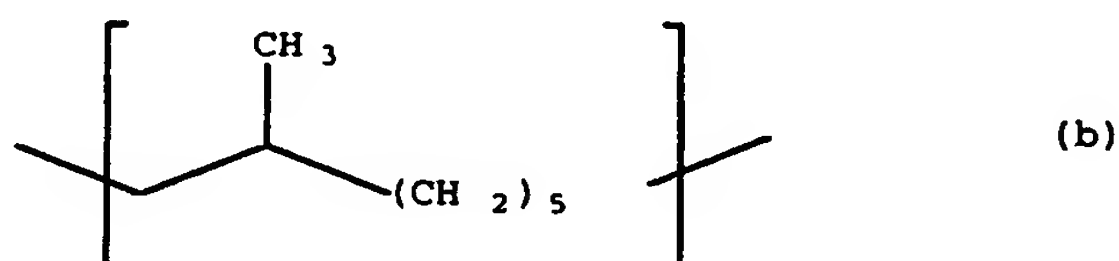
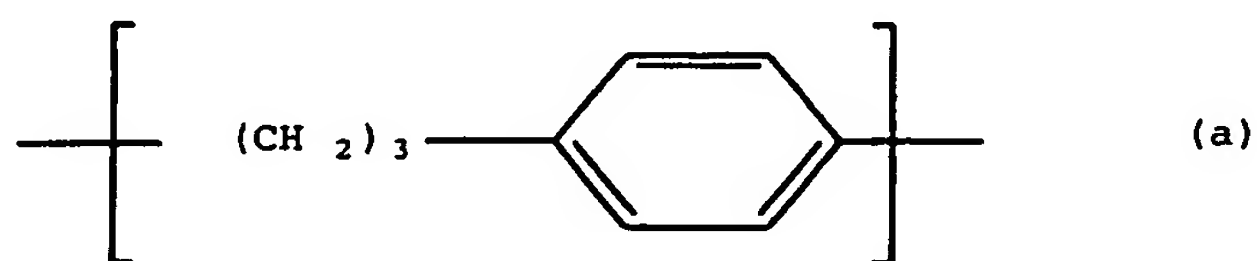
The words, "acid linker" refer to a divalent
linking group symbolized as, -(L_a)-, which has the
function of joining the 5 position of the indole nucleus
10 to an acidic group in the general relationship:



The words, "acid linker length", refer to the number
of atoms (excluding hydrogen) in the shortest chain of the
15 linking group -(L_a)- that connects the 5 position of the

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indole nucleus with the acidic group. The presence of a carbocyclic ring in $-(L_a)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_a)-$. Illustrative acid linker groups are;



wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

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The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals, $-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-$.

5

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_3$; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, and $-\text{CH}=\text{CH}_2$.

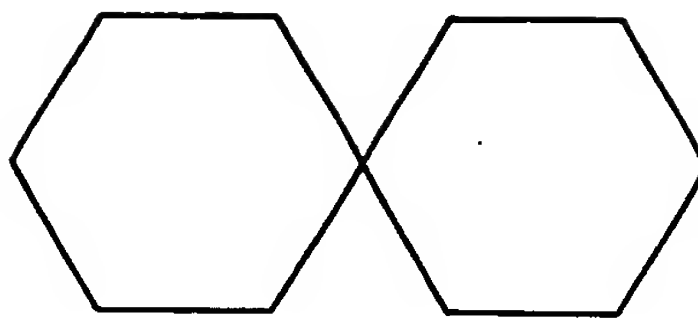
20

The term "oxime amide" means the radical,
 $-\text{C}=\text{NOR}-\text{C}(\text{O})\text{NH}_2$

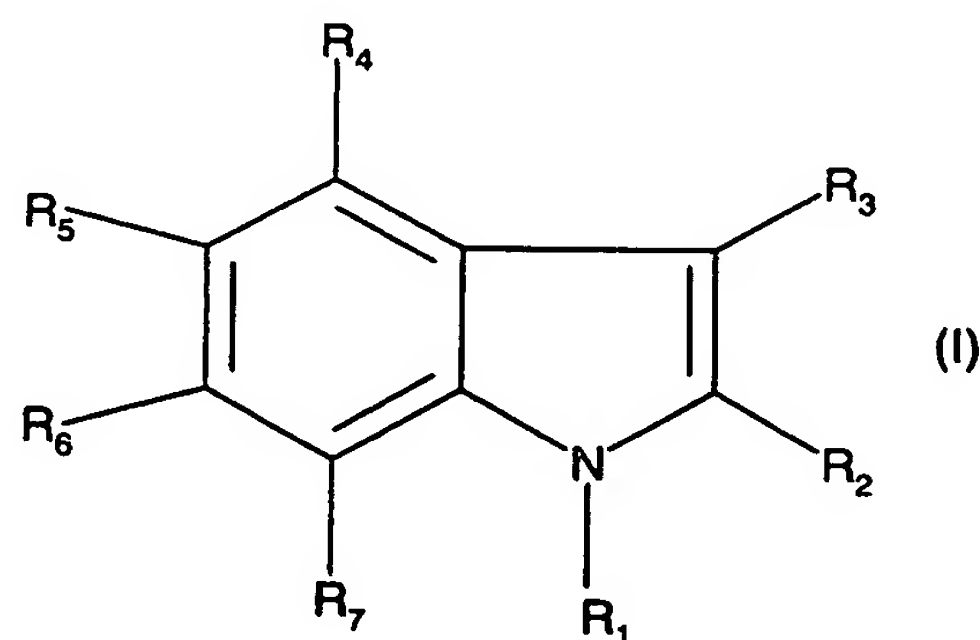
The term "thio-oxime amide" means the radical
 $-\text{C}=\text{NOR}-\text{C}(\text{S})-\text{NH}_2$.

The term "spiro[5.5]undecanyl" refers to the group
represented by the formula;

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**II. The amino acid 1H-indole Compounds of the Invention:**

The present invention provides novel classes of
5 indole compounds useful as sPLA2 inhibitors for the
treatment of inflammation. Classes of indole compounds
of this invention include indole glyoxylamide amino acid
derivatives, indole-3-oxime amide amino acid derivatives
and indole acetamide amino acid derivatives. The
10 compounds of the invention have the general formula (I)
or a pharmaceutically acceptable salt, solvate or
prodrug thereof;



15

wherein ;

 R_1 is selected from groups (a), (b), and (c)

wherein;

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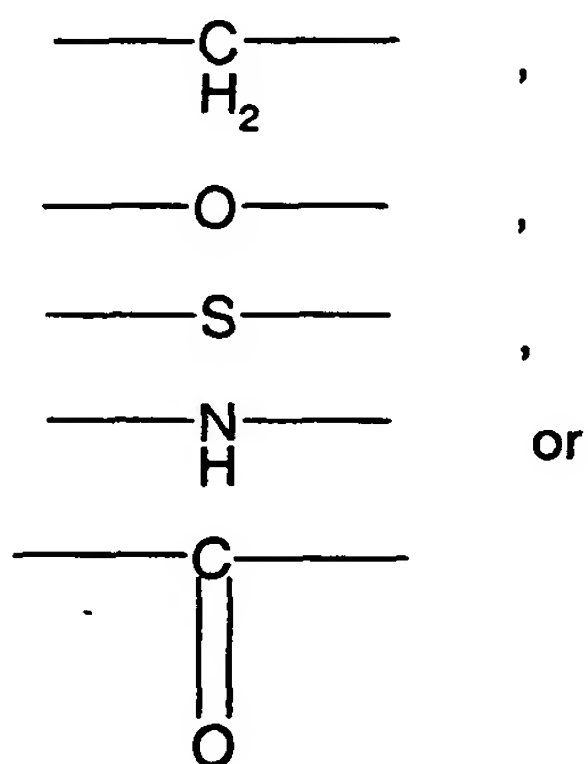
(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or
5 more independently selected non-interfering substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

10 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

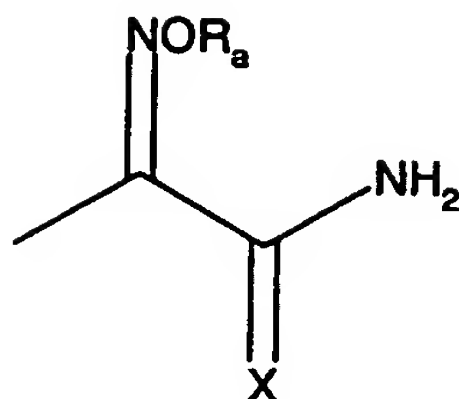
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:



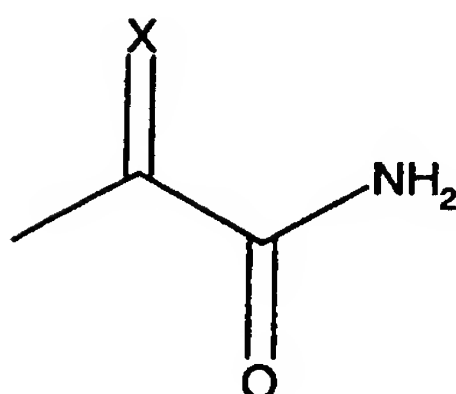
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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,

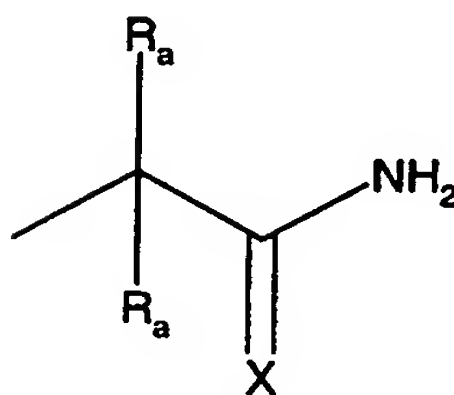
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or



or



5

wherein X is oxygen or sulfur, R_a is independently selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

R_4 is the group, $-(L_C)-(acylamino\ acid\ group)$;
 10 wherein $-(L_C)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein
 $-(L_a)-$, is an acid linker having an acid linker length
 15 of 1 to 8.

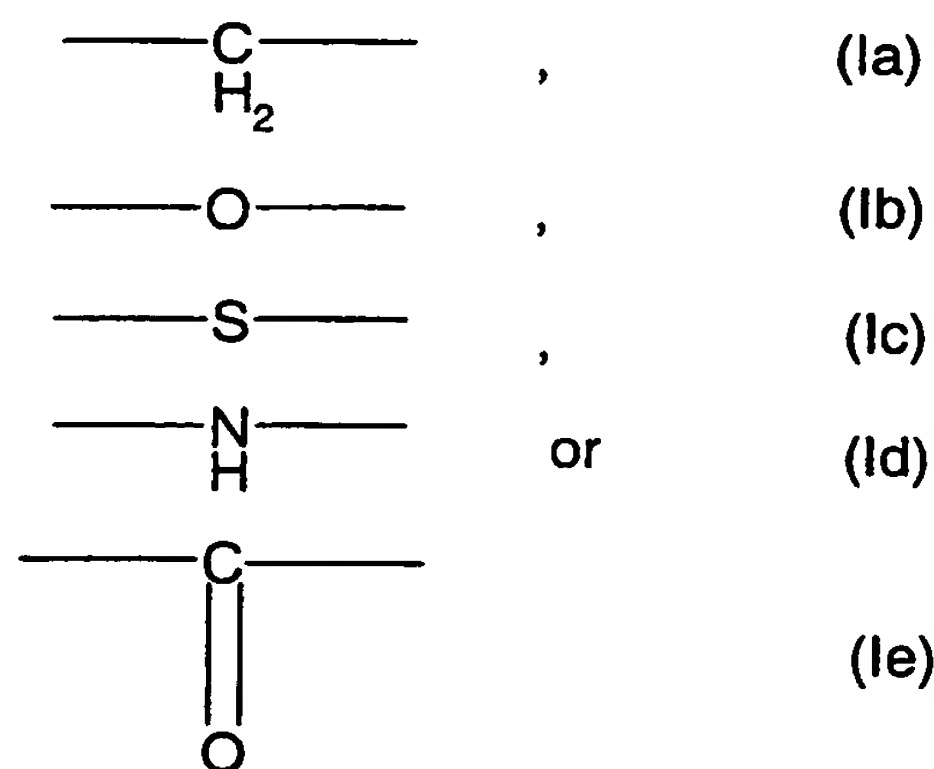
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R₆ and R₇ are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

Preferred Subgroups of Compounds of Formula (I):
Preferred R₁ substituents:

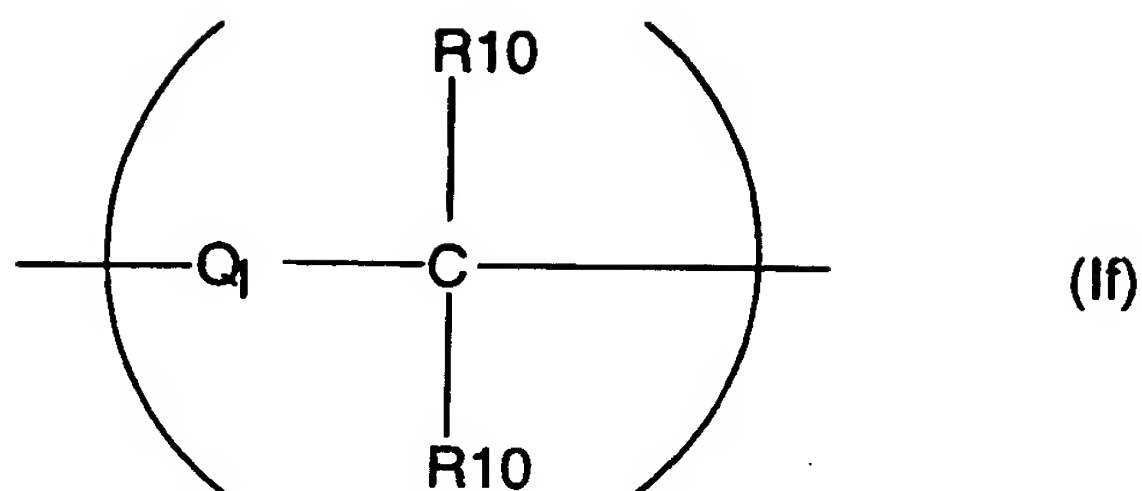
A preferred subclass of compounds of formula (I) are those where for R₁ the divalent linking group -(L₁)- is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



15

or

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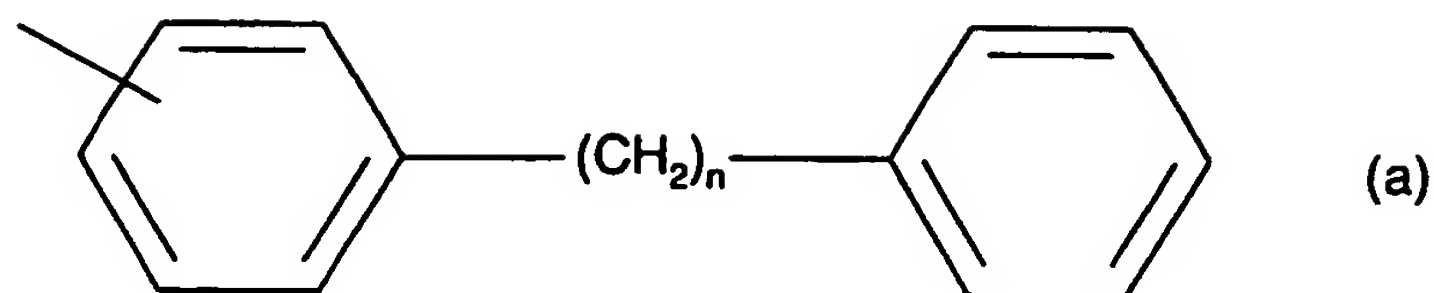
where Q_1 is a bond or any of the divalent groups (Ia),
 (Ib), (Ic), (Id), (Ie), and (If) and each R_{10} is
 5 independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl or
 C_{1-8} alkoxy.

Particularly preferred as the linking group $-(\text{L}_1)-$ of
 R_1 is an alkylene chain of 1 or 2 carbon atoms, namely,
 10 $-(\text{CH}_2)-$ or $-(\text{CH}_2-\text{CH}_2)-$.

The preferred group for R_{11} is a substituted or
 unsubstituted group selected from the group consisting of
 C_5-C_{14} cycloalkyl, C_5-C_{14} cycloalkenyl, phenyl, naphthyl,
 15 norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
 indenyl, stilbenyl, terphenyl, diphenylethylenyl,
 phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
 biphenyl, bibenzylyl and related bibenzylyl homologues
 represented by the formula (a);

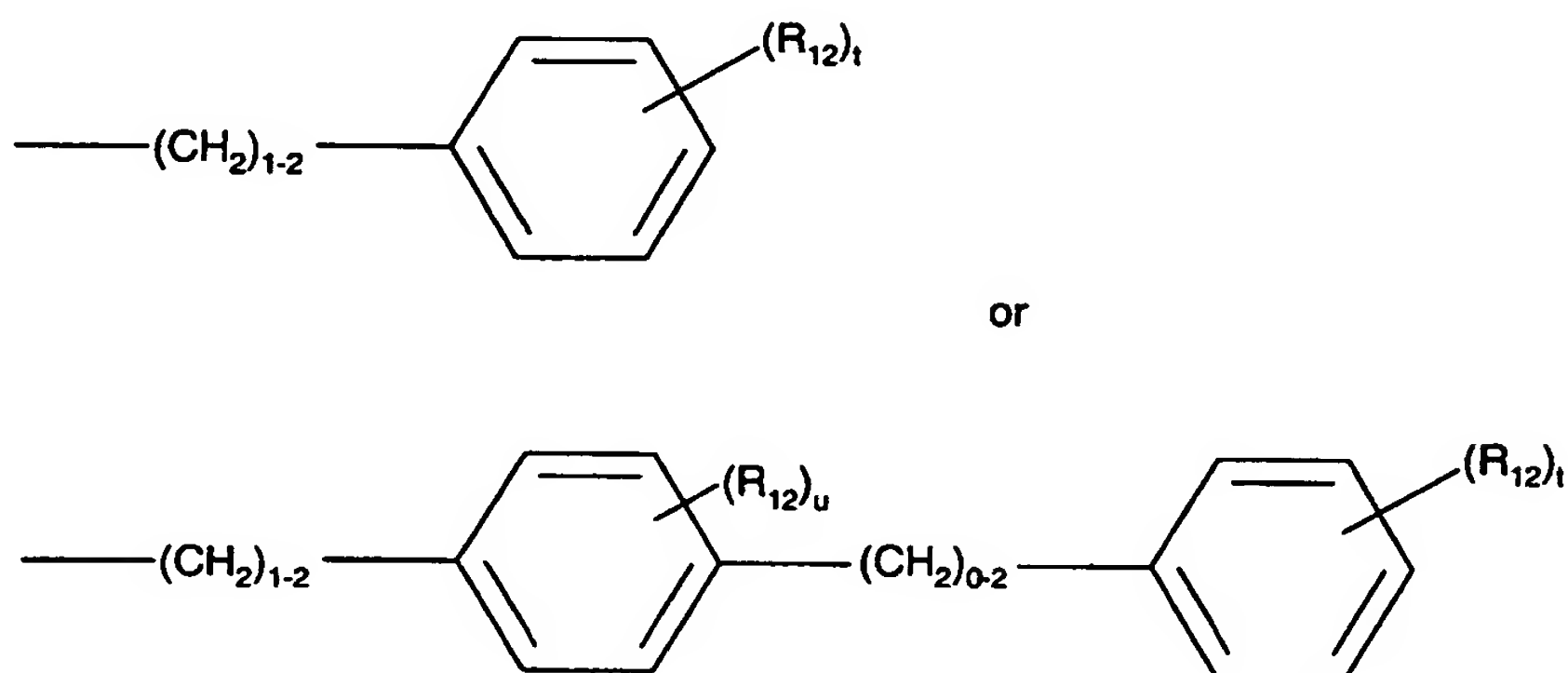
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-21-



where n is a number from 1 to 8.

Particularly preferred are compounds wherein for R₁
 5 the combined group -(L₁)-R₁₁ is selected from the group
 consisting of

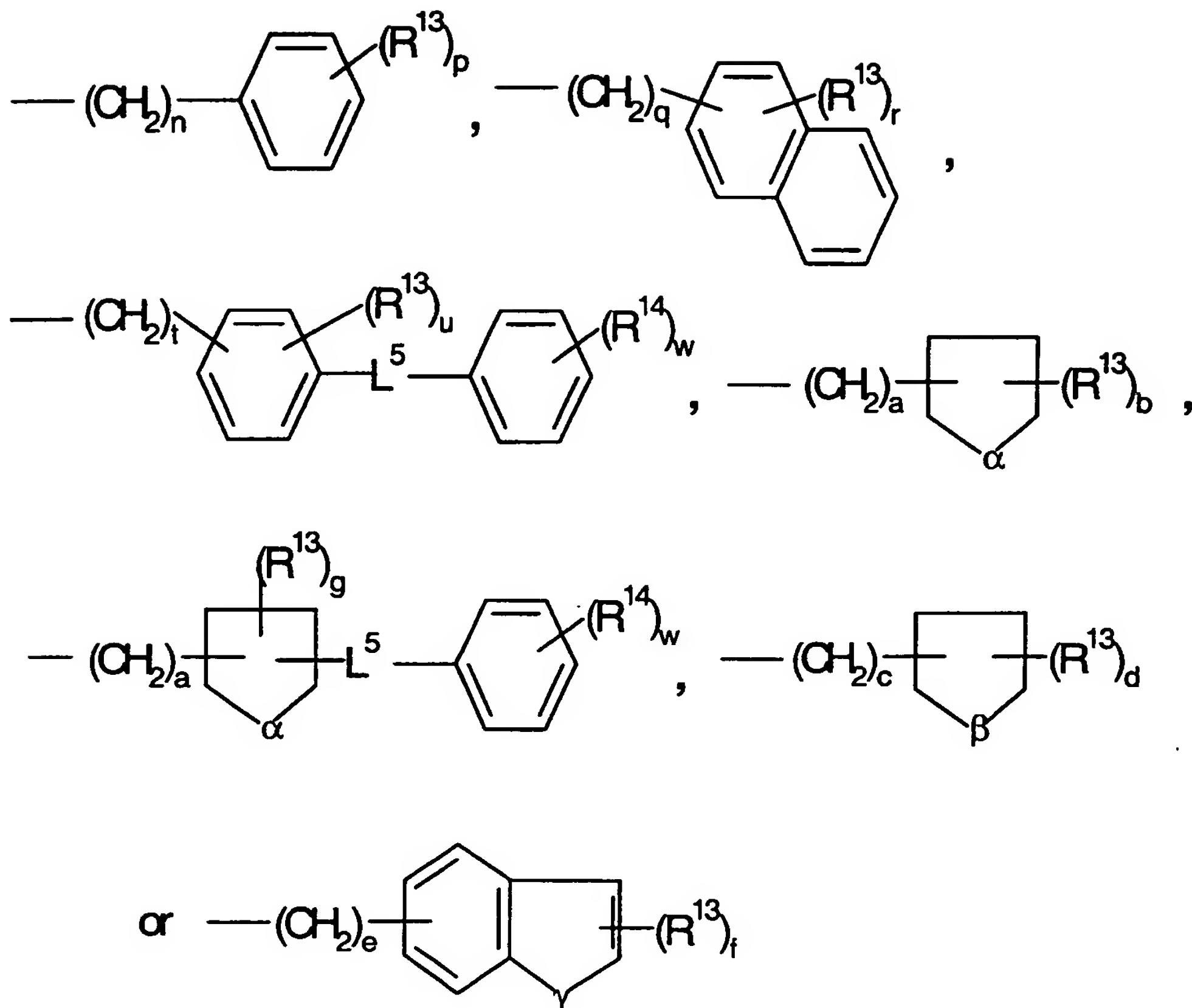


where R₁₂ is a radical independently selected from halo,
 C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), -O-(C₁-C₈
 10 alkyl) and C₁-C₈ haloalkyl where t is a number from 0 to
 5 and u is a number from 0 to 4 is the group -(L₁)-R₁₁;
 where, -(L₁)- is a divalent linking group of 1 to 8
 atoms and where R₁₁ is a group selected from (a) or (b).

15 Preferred for R₁₁ is -(CH₂)_m-R¹² wherein m is an
 integer from 1 to 6, and R¹² is (d) a group represented by
 the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8

5 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$,

$-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur

10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer

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from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

5

Preferred R_2 substituents:

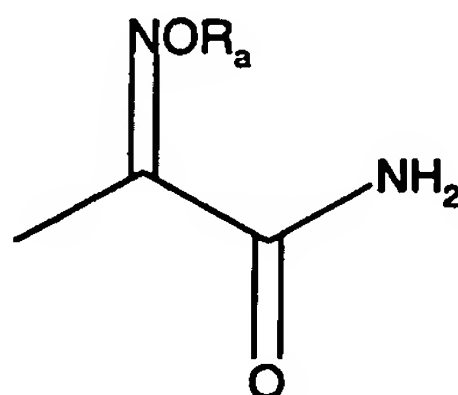
R_2 is preferably selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, $-O-(C_1-C_3$ alkyl),

10 $-S-(C_1-C_3$ alkyl), $-C_3-C_4$ cycloalkyl $-CF_3$, halo, $-NO_2$, $-CN$, $-SO_3$. Particularly preferred R_2 groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-F$, $-CF_3$, $-Cl$, $-Br$, or $-O-CH_3$.

15 **Preferred R_3 substituents:**

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

Another preferred subclass of compounds of
20 formula (I) are those wherein Z is an oxime amide group.



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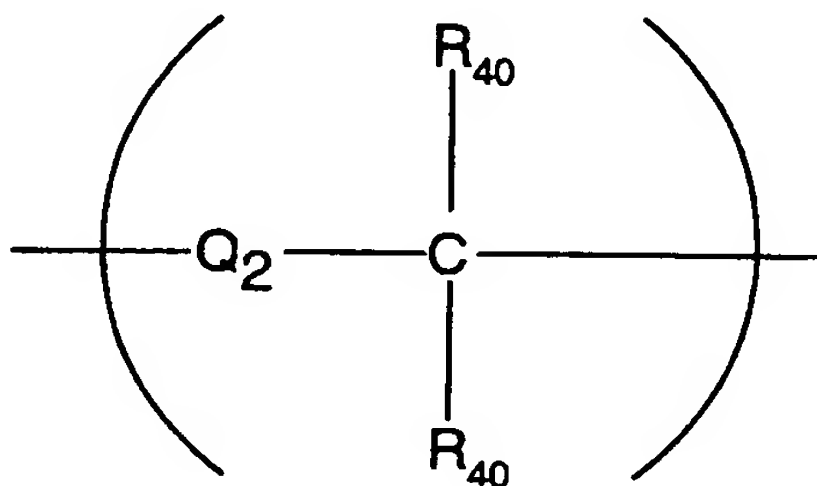
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Also preferred are compounds of formula (I) wherein R_3 is an oxime amide group and R_a is hydrogen, methyl or ethyl. For the group R_3 it is preferred that the linking group $-(L_3)-$ be a bond.

5

Preferred R_4 substituents:

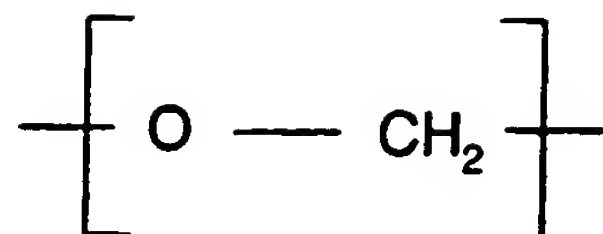
Another preferred subclass of compounds of formula (I) are those wherein R_4 is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, $-(L_C)-$, for R_4 is selected from a group represented by the formula;



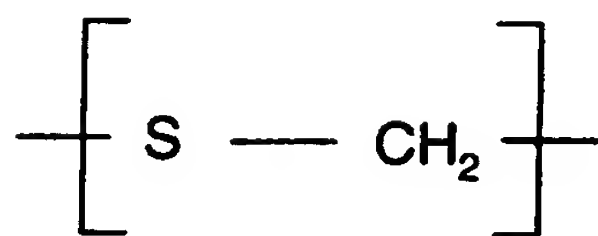
where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$, $-C(O)-$, and $-S-$, and each R_{40} is independently selected from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8 alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, $-(L_C)-$, for R_4 is selected from the specific groups;

20

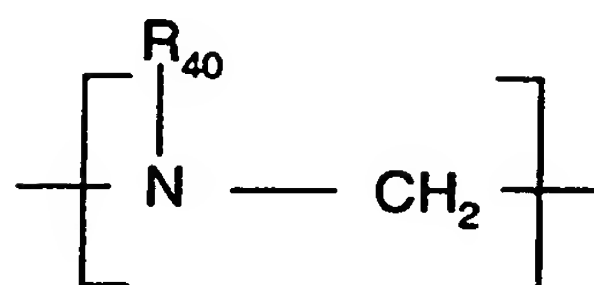
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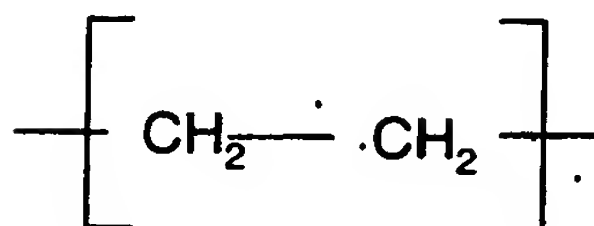
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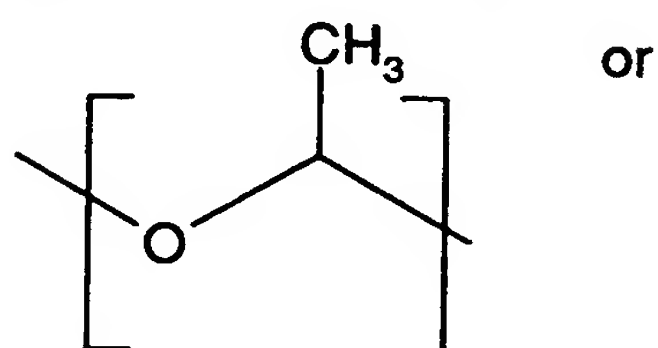
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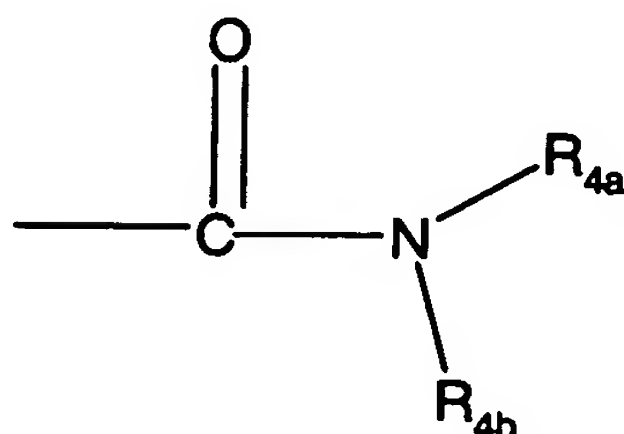
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,

where R_{40} is hydrogen or C_1 - C_8 alkyl.

Preferred as the (acylamino acid group) in the group R_4
5 is the group:



,

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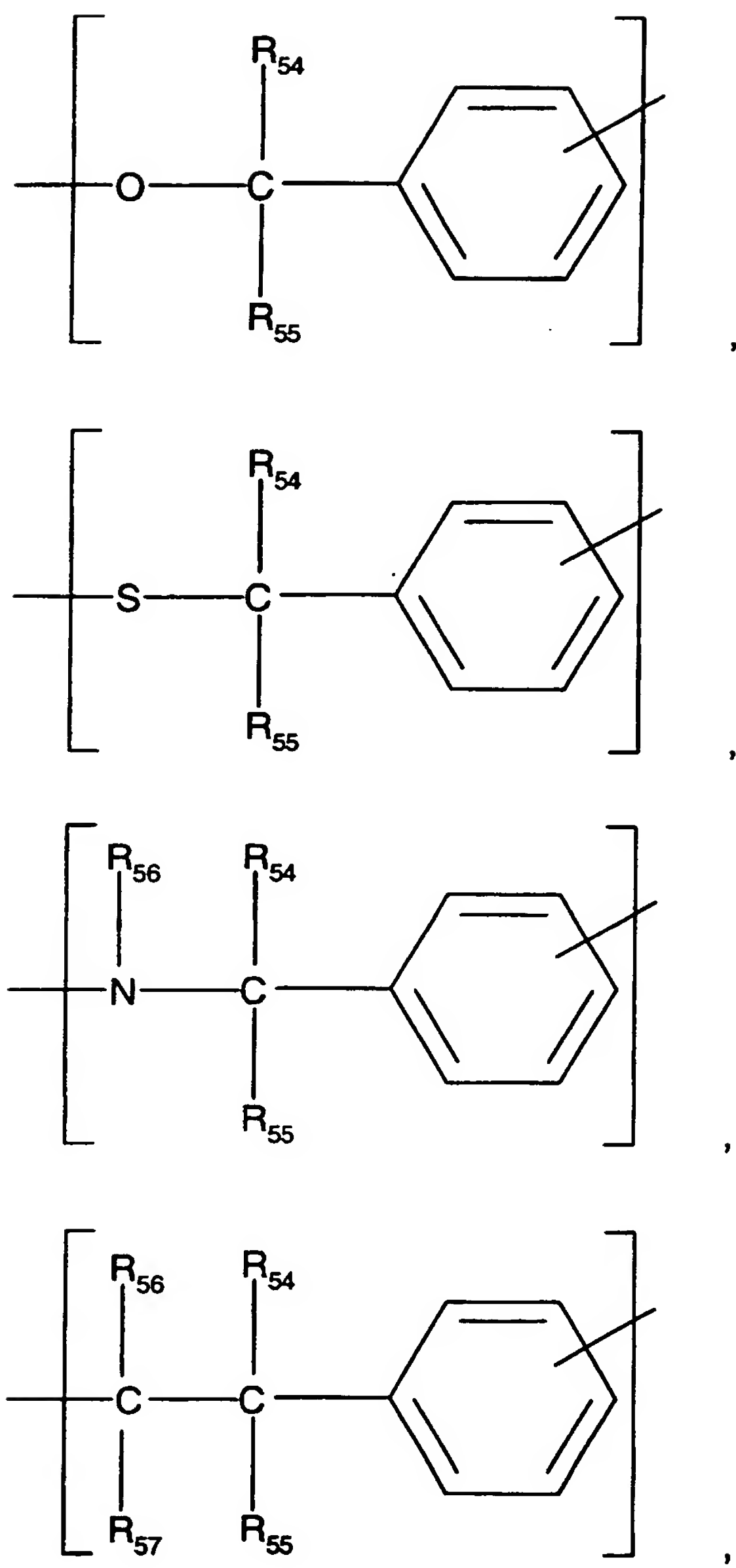
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wherein R^{4a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof. A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

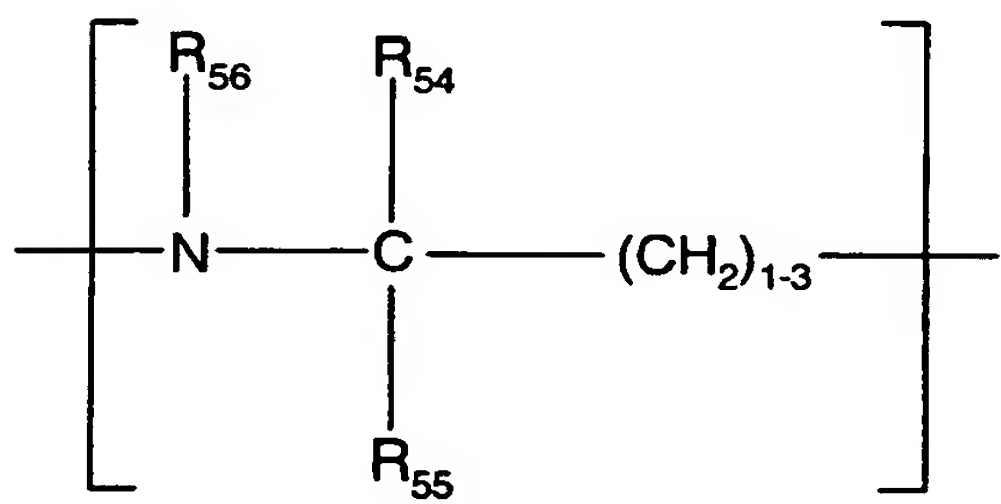
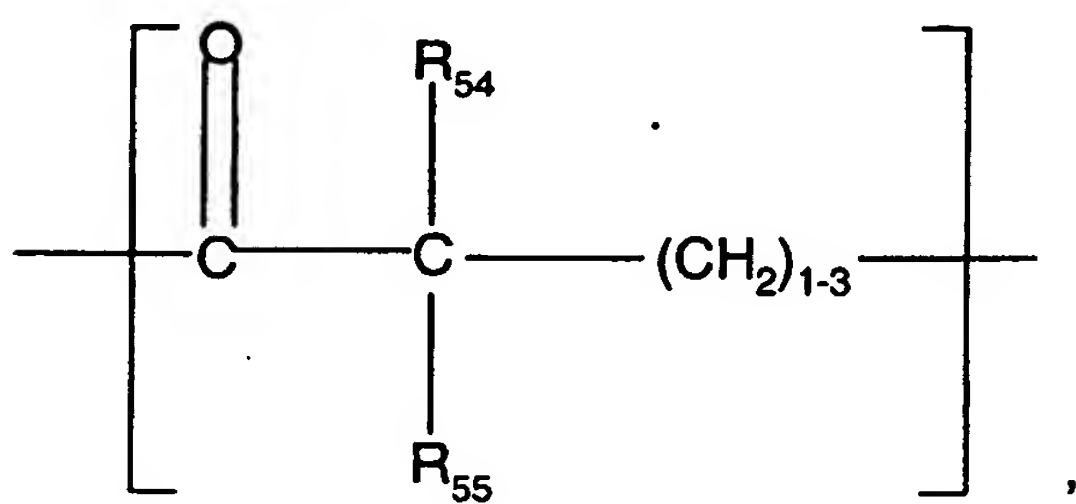
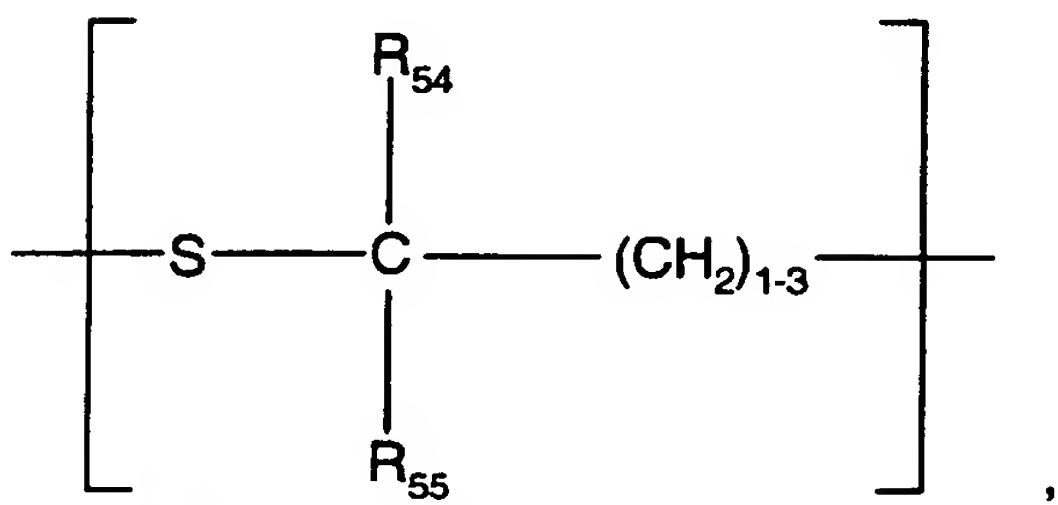
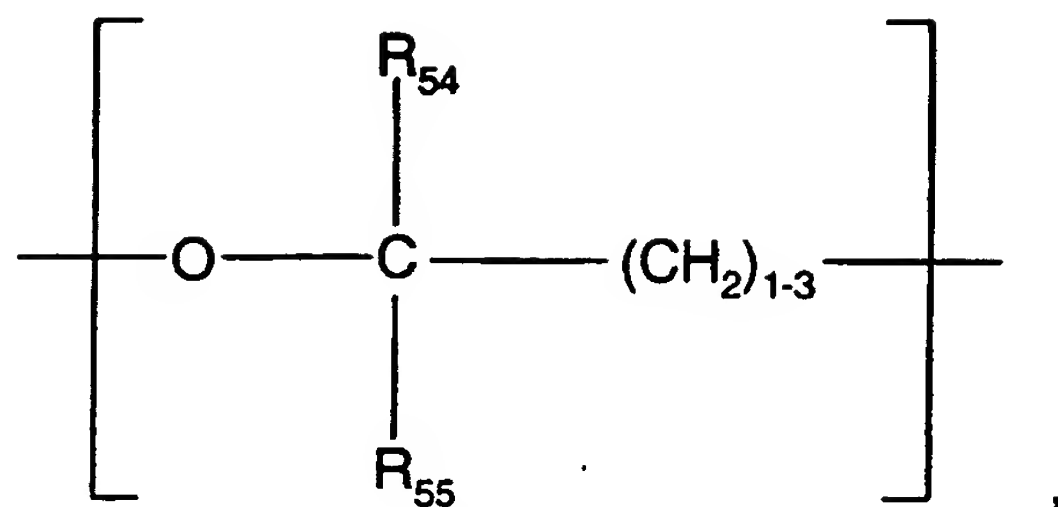
Particularly preferred are R^{4b} groups that combine with the nitrogen atom to represent amino acid residues from the amino acid groups selected from: glycine, glycine methyl ester, L-alanine, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L-valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

Preferred R_5 Substituents:

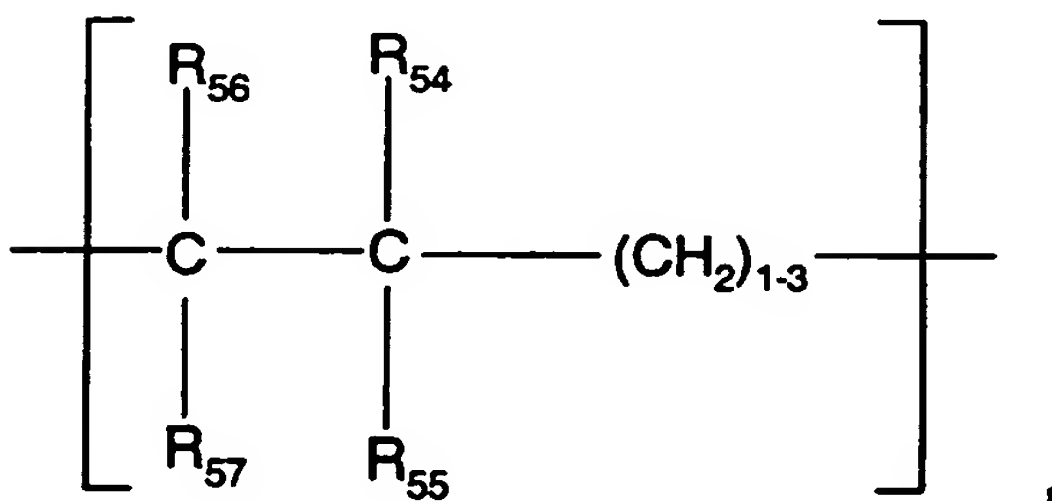
Preferred acid linker, $-(L_a)-$, for R_5 is selected from the group consisting of;



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and



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wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo. Preferred (acidic group) for R₅ is selected from the group consisting of -CO₂H, -SO₃H and

5 -P(O)(OH)₂.

Preferred R₆ and R₇ substituents:

Another preferred subclass of compounds of formula (I) are those wherein for R₆ and R₇ the non-

10 interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆

15 alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆

20 alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆ haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H,

25 chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,

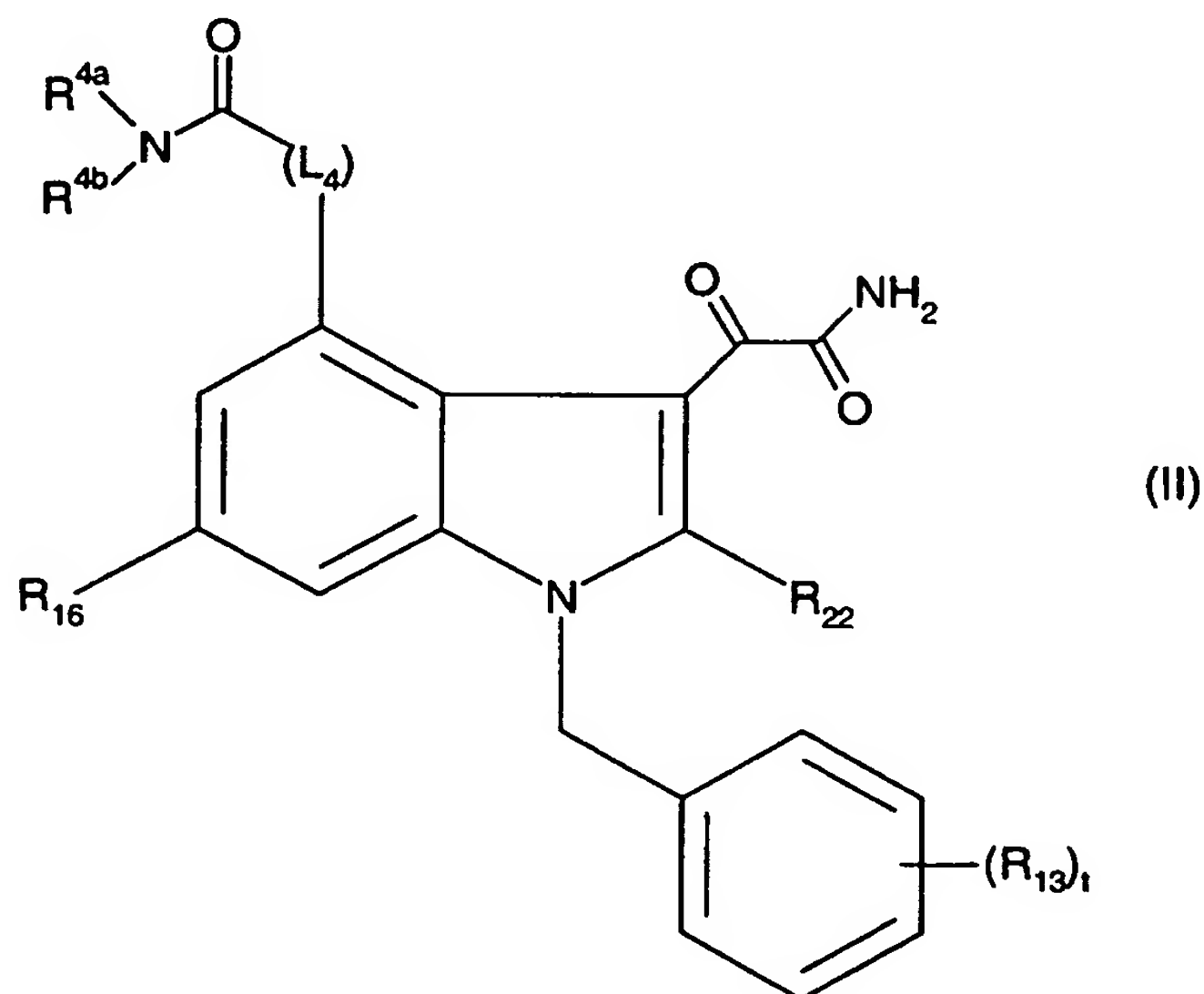
-30-

iodo, nitro, phosphono, $-\text{SO}_3\text{H}$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

Most preferred as non-interfering substituents are
5 methyl, ethyl, propyl, and isopropyl.

Preferred compounds of the invention are those
having the general formula (II), or a pharmaceutically
acceptable salt, solvate or prodrug derivative thereof;

10



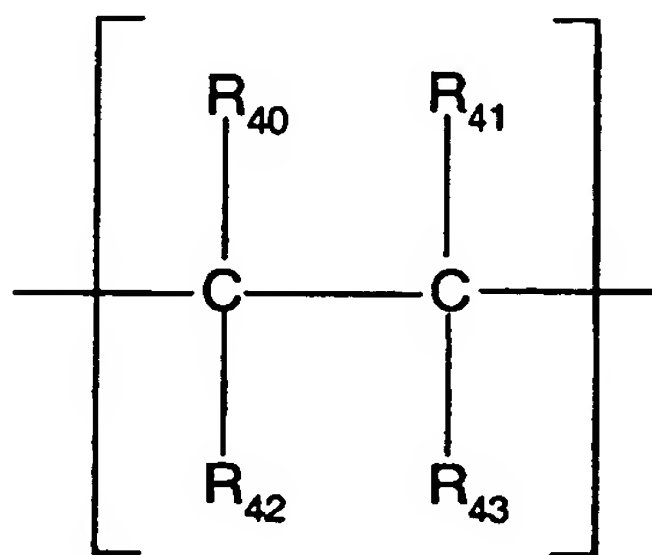
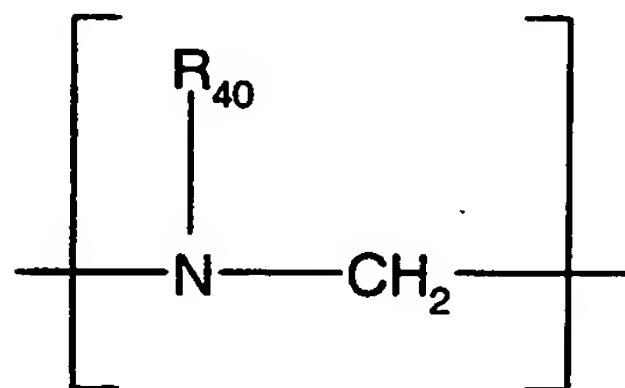
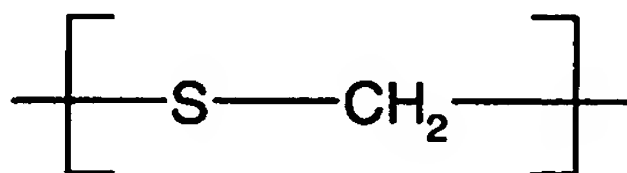
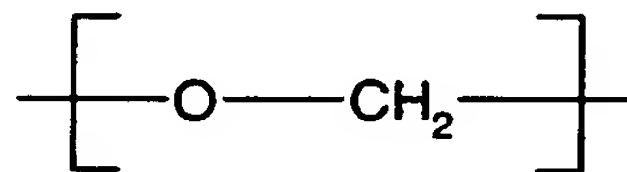
wherein ;

15 R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-\text{F}$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, or $-\text{O}-\text{CH}_3$;

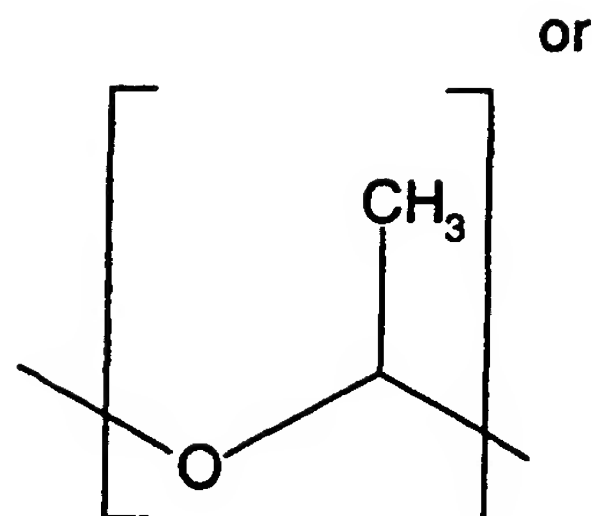
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wherein R^{4a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H); and - (L₄)- is a divalent group selected from;



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where R_{40} , R_{41} , R_{42} , and R_{43} are each independently selected from hydrogen or C_1 - C_8 alkyl.

R_{16} is selected from hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_1 - C_8 alkylthio C_1 - C_8 haloalkyl, C_1 - C_8 hydroxyalkyl, and halo.

R_{13} is selected from hydrogen and C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, C_1 - C_8 haloalkyl, C_1 - C_8 phenyl, halophenyl, hydroxyalkyl, and halo, and t is an integer from 0 to 5.

Preferred specific compounds (and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof) which are illustrative of the compounds of the invention are as follow:

N -[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

N -[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]glycine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

5 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

10 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

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The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups
5 various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium,
10 magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

15 Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous
20 bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable
25 organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,

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bitartrate, borate, bromide, camsylate, carbonate,
chloride, clavulanate, citrate, chloride, edetate,
edisylate, estolate, esylate, fluoride, fumarate,
gluceptate, gluconate, glutamate, glycolylarsanilate,
5 hexylresorcinate, bromide, chloride, hydroxynaphthoate,
iodide, isothionate, lactate, lactobionate, laurate,
malate, malseate, mandelate, mesylate, methylbromide,
methylnitrate, methylsulfate, mucate, napsylate, nitrate,
oleate, oxalate, palmitate, pantothenate, phosphate,
10 polygalacturonate, salicylate, stearate, subacetate,
succinate, tannate, tartrate, tosylate, trifluoroacetate,
trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or
15 more chiral centers and may thus exist in optically active
forms. Likewise, when the compounds contain an alkenyl or
alkenylene group there exists the possibility of cis- and
trans- isomeric forms of the compounds. The R- and S-
isomers and mixtures thereof, including racemic mixtures
20 as well as mixtures of cis- and trans- isomers, are
contemplated by this invention. Additional asymmetric
carbon atoms can be present in a substituent group such as
an alkyl group. All such isomers as well as the mixtures
thereof are intended to be included in the invention. If
25 a particular stereoisomer is desired, it can be prepared
by methods well known in the art by using stereospecific

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reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

5 For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can

10 be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable

15 groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative

20 form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid

25 derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides

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prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

10

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

15

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

20

a) The 1H-indole-3-glyoxylamide amino derivative compounds of the invention are prepared by room temperature base catalyzed condensation of the amino acid protected at the acid terminus by protecting group

25

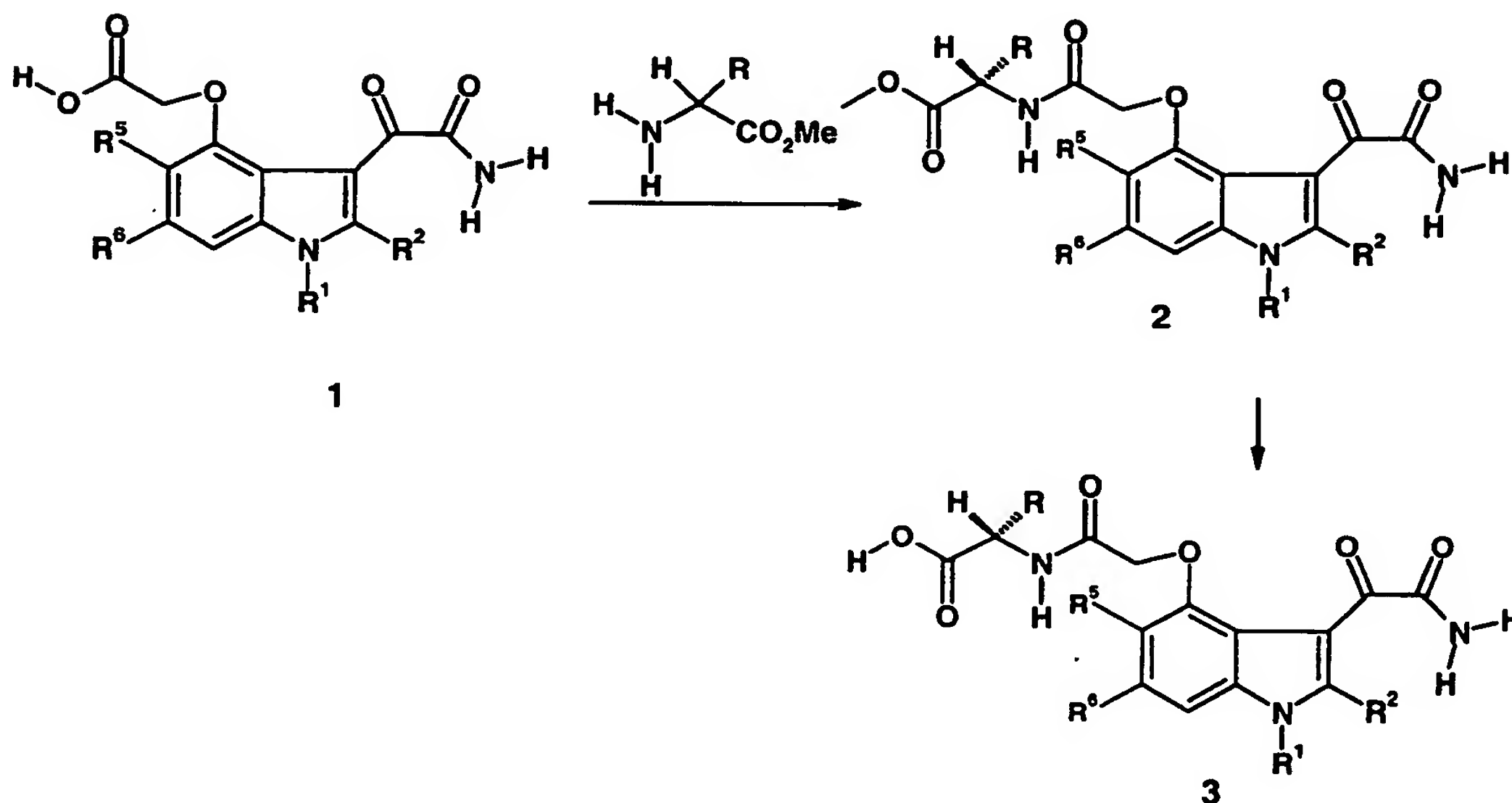
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known in the literature but preferably as the methyl ester with the 1H-indole-3-glyoxylamide acid derivative compound of formula (1) as shown in Scheme I:

5

Scheme 1



Typically, the condensation or coupling is performed in a solvent such as dimethyl formamide, tetrahydrofuran or aqueous mixtures of the like. In general protic solvents are preferred for the purpose of this invention. The reaction is catalyzed by a base including weak organic or inorganic bases. Organic bases such as collidine are preferred. The reaction is also preferably run in the presence of agents that retard or reduce racemization of the amino acid or its

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derivative, such as for example, benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate.

Upon completion of the reaction, the mixture is concentrated in vacuo. The resulting product mixture is
5 chromatographed to obtain the target compound.

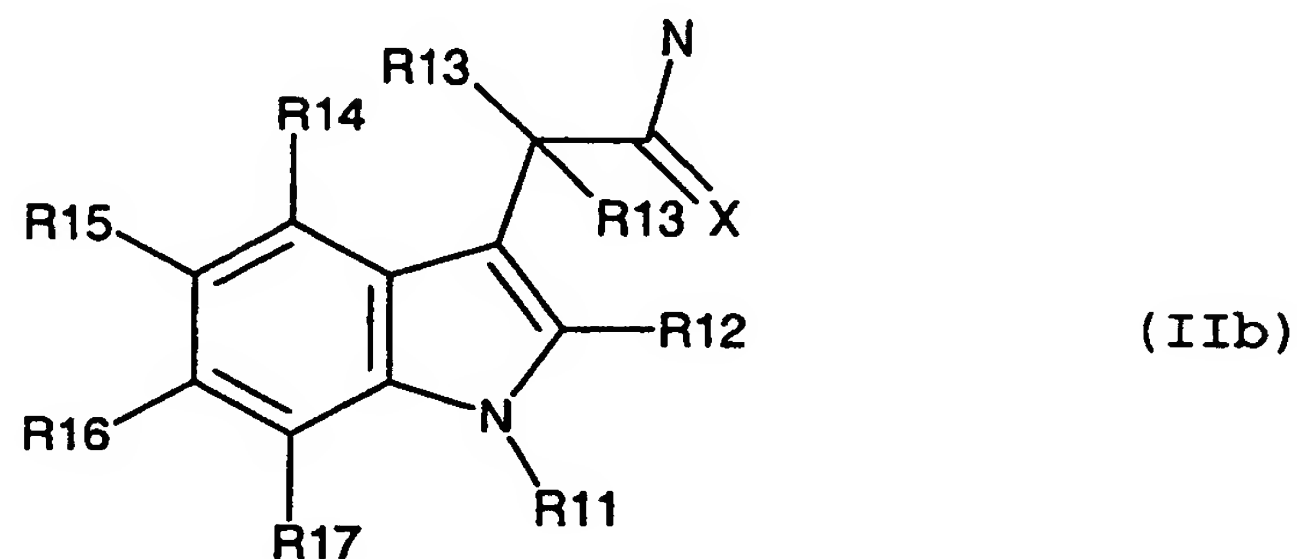
One of skill in the art is aware that the derivatives of the acid such as the acid salt or the methyl ester of the acid, can be reacted with the amino acid or
10 derivatives thereof to obtain the protected compound 2 or a corresponding derivative. Such methods are well known in the arts and can be found in reference texts such as for example J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y., 1985, and R. C.
15 Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y., 1989. The protected compounds of formula (2) are also useful sPLA₂ inhibitors and are also compounds of this invention.

20 b) 1H-indole-3-acetamide amino acid derivative
sPLA₂ inhibitors are similarly prepared by condensation of the protected amino acid with the 1H-indole-3-acetamide sPLA₂ inhibitor. The 1H-indole-3-acetamide sPLA₂ inhibitors and methods of making them are set out in U.S.
25 Patent No. 5,684,034, the entire disclosure of which is incorporated herein by reference. Indole-3-acetamide

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amino acid derivative sPLA2 inhibitors of this invention are represented by compounds of formula (IIb), and pharmaceutically acceptable salts and prodrug derivatives thereof,



5

wherein ;

X is oxygen or sulfur;

R₁₁ is selected from groups (i), (ii) (iii) and (iv)

10 where;

(i) is C₆-C₂₀ alkyl, C₆-C₂₀ alkenyl, C₆-C₂₀ alkynyl, C₆-C₂₀ haloalkyl, C₄-C₁₂ cycloalkyl, or

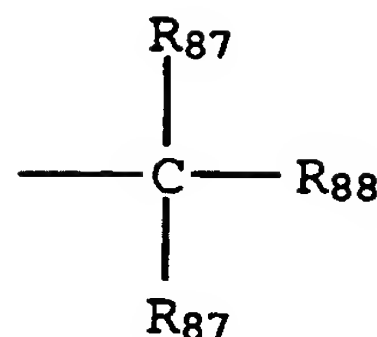
(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C₁-C₁₀ alkyl, C₁-C₁₀ alkylthio, C₁-C₁₀ alkoxy, carboxyl, amino, or hydroxyamino; or

(iii) is -(CH₂)_n-(R₈₀), or -(NH)-(R₈₁), where n is 1 to 8, and R₈₀ is a group recited in (i), and R₈₁ is selected from a group recited in (i) or (ii);

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(iv) is



where R₈₇ is hydrogen or C₁-C₁₀ alkyl, and R₈₈ is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C₁-C₁₀ alkylthio, C₁-C₁₀ alkoxy, phenyl, nitro, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

R₁₂ is halo, C₁-C₂ alkylthio, C₁-C₂ alkyl, C₁-C₂ alkyaryl or C₁-C₂ alkoxy;

each R₁₃ is independently hydrogen, halo, or methyl;

R¹⁴ is the group -L_C-[acylamino acid], wherein the acylamino acid group is -C(O)-NR^{14a}R^{14b} wherein R^{14a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl; and -L_C- is as defined *supra*, and wherein NR^{14b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. Most preferred are compounds of formula II wherein the group R^{14a} is a hydrogen atom (H). A preferred source of the amino acid residue NR^{14b} is an amino acid selected from the group comprising isoleucine, valine, phenylalanine,

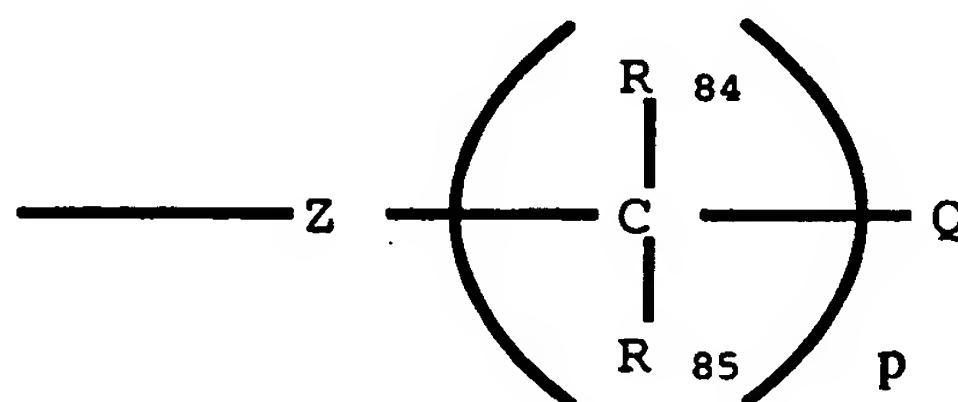
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aspartic acid, leucine, glycine and isomers and derivatives thereof;

R_{15} is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein
 5 $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

R_{16} and R_{17} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in
 10 the set R_{15} , R_{16} , and R_{17} , combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, $-SH$, $-CN$,
 15 C_1-C_{10} alkylthio, arylthio, thioacetal, $-C(O)O(C_1-C_{10} alkyl)$, hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5- to 8-
 20 membered heterocyclic ring; or a group having the formula;



where,

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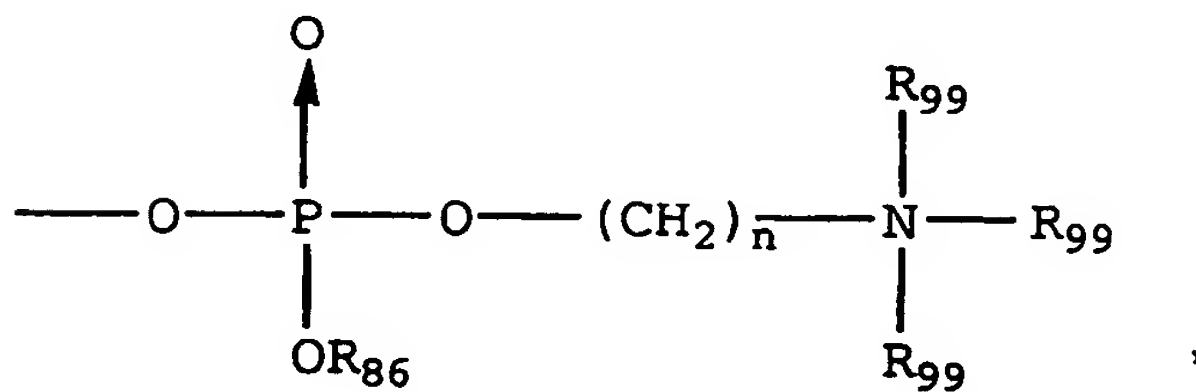
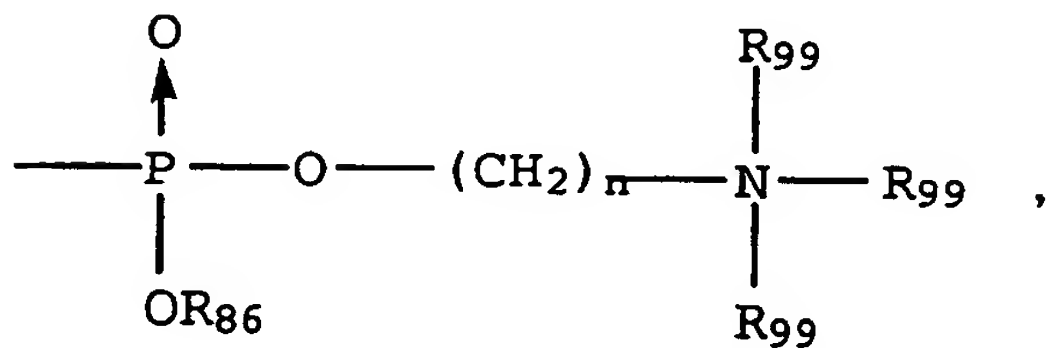
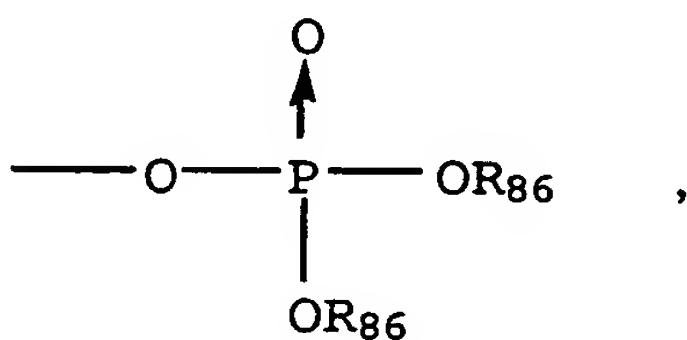
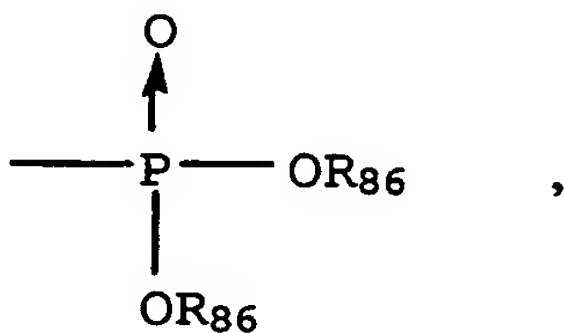
R₈₄ and R₈₅ are each independently selected from hydrogen, C₁-C₁₀ alkyl, hydroxy, or R₈₄ and R₈₅ taken together are =O;

p is 1 to 5,

5 Z is a bond, -O-, -N(C₁-C₁₀ alkyl)-, -NH-, or -S-;

and

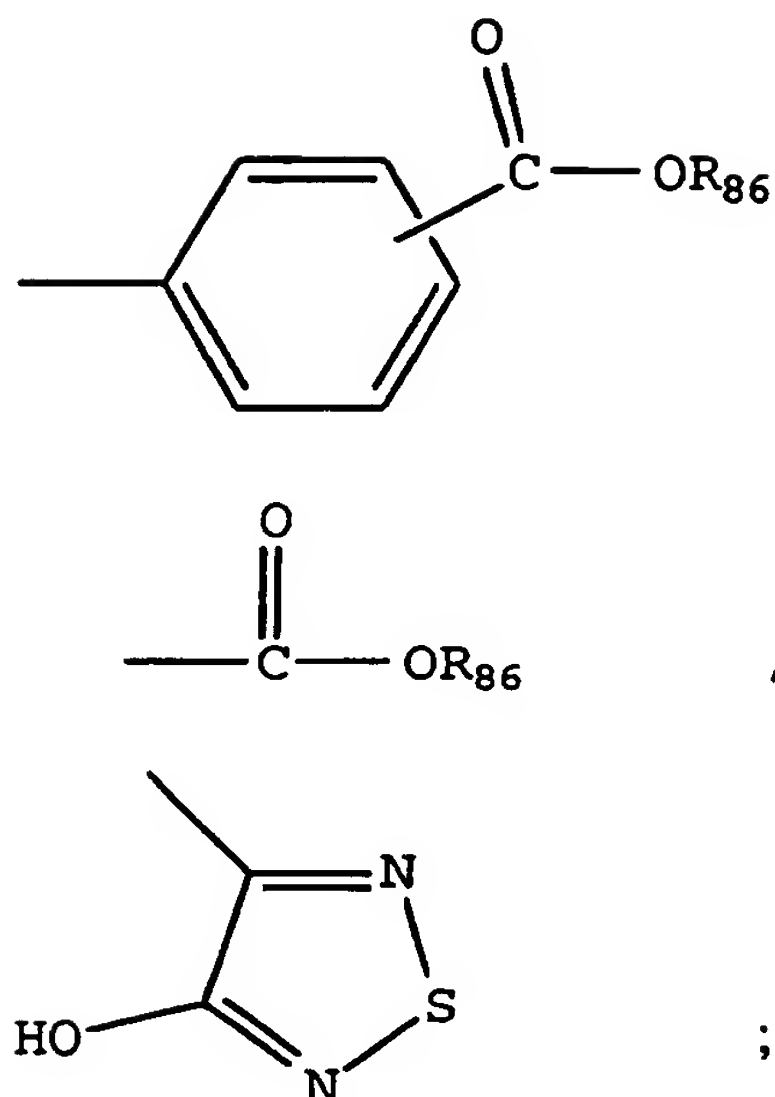
Q is -CON(R₈₂R₈₃), -5-tetrazolyl, -SO₃H,



10

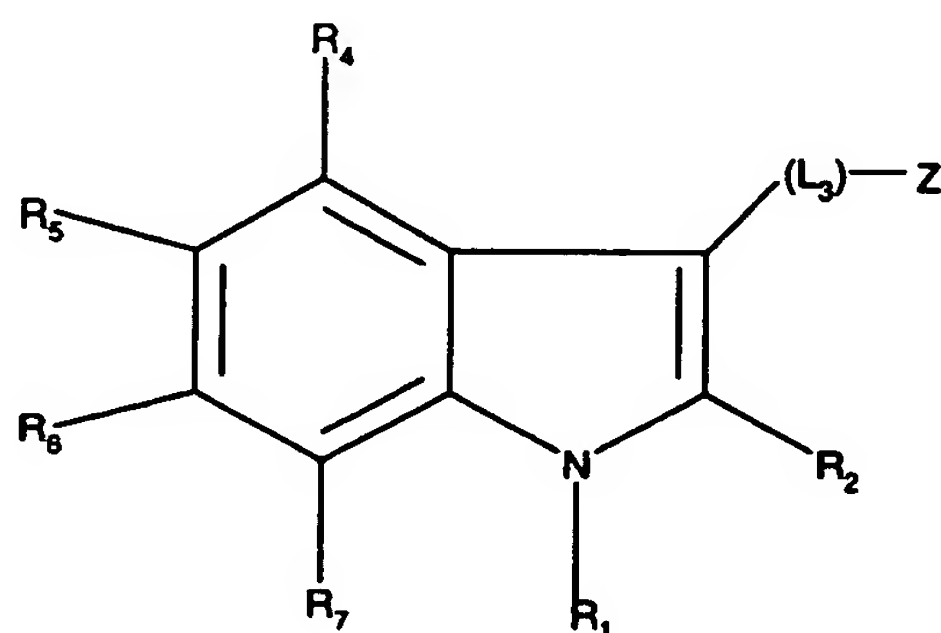
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where n is 1 to 8, R₈₆ is independently selected from hydrogen, a metal, or C₁-C₁₀ alkyl, and R₉₉ is selected
 5 from hydrogen or C₁-C₁₀ alkyl.

c) Indole-3-Oxime amide compounds of the invention are represented by compounds of formula (III) or a
 pharmaceutically acceptable salt, solvate or prodrug
 10 thereof;



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wherein ;

R_1 is selected from groups (a), (b), and (c)

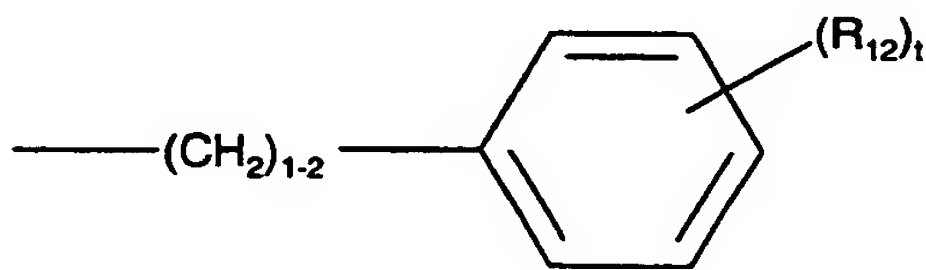
wherein;

5 (a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

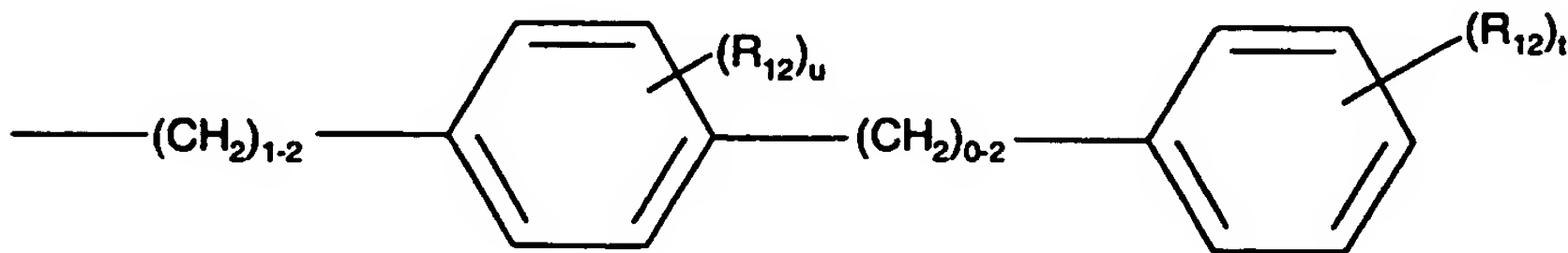
(b) is a member of (a) substituted with one or more independently selected non-interfering
10 substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b).

15 Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of



or



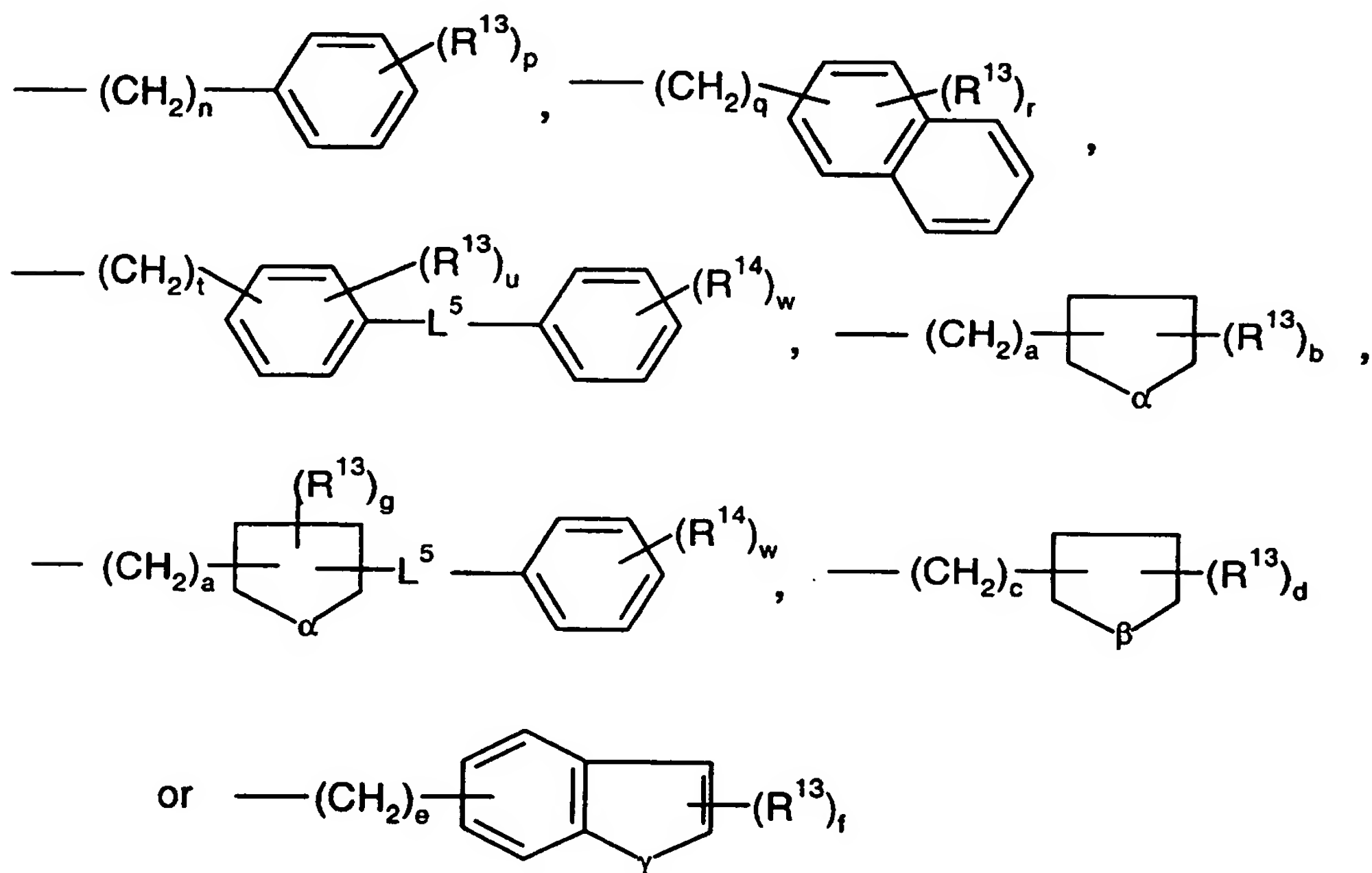
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where R_{12} is a radical independently selected from halo, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8 \text{ alkyl})$ and C_1 - C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

5

Also preferred for R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by the formula:



10

wherein a , c , e , n , q , and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to

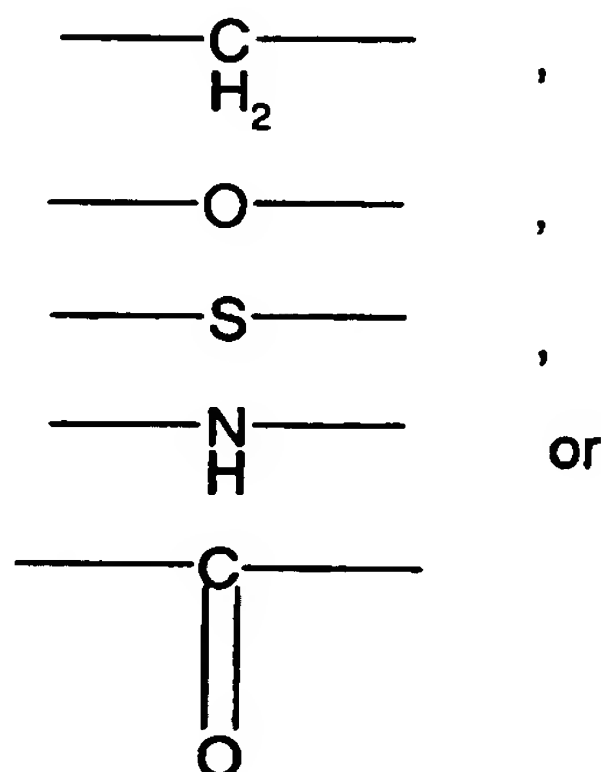
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C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$, $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f , p , and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

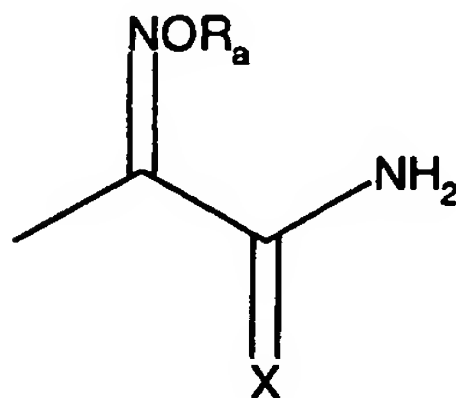
$-(L_3)-Z$, is the group where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:



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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



5

wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R₄ is the group, -(L_C)-(acylamino acid group); wherein -(L_C)-, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

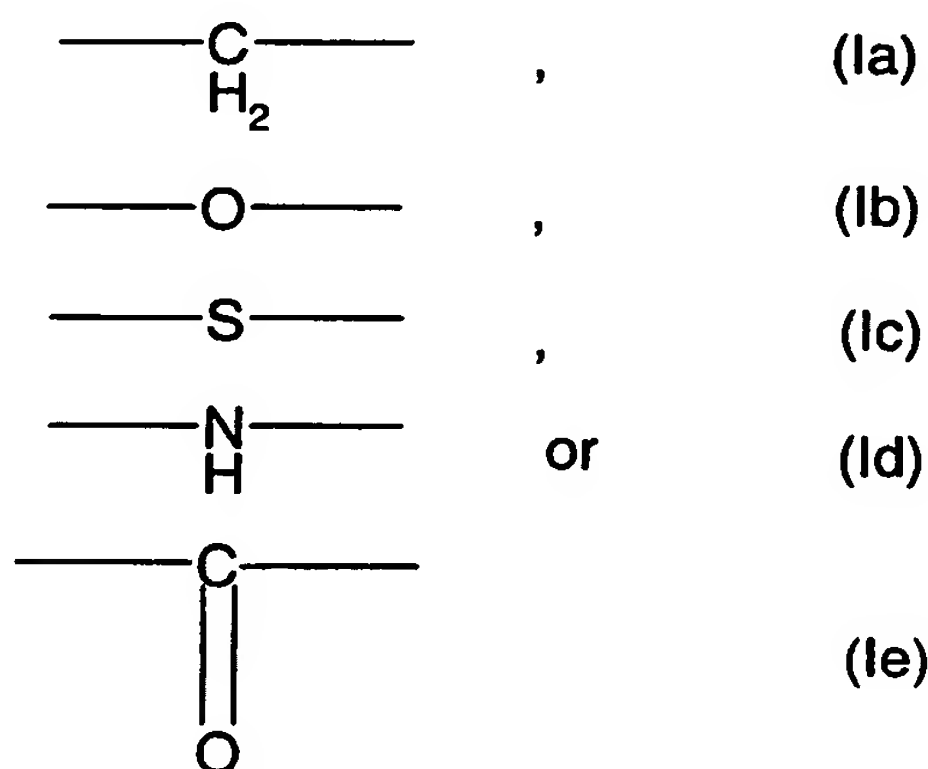
R₅ is selected from hydrogen, a non-interfering substituent, or the group, -(L_a)-(acidic group); wherein
15 -(L_a)-, is an acid linker having an acid linker length of 1 to 8.

R₆ and R₇ are selected from hydrogen, non-interfering substituent, carbocyclic radical,
20 carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

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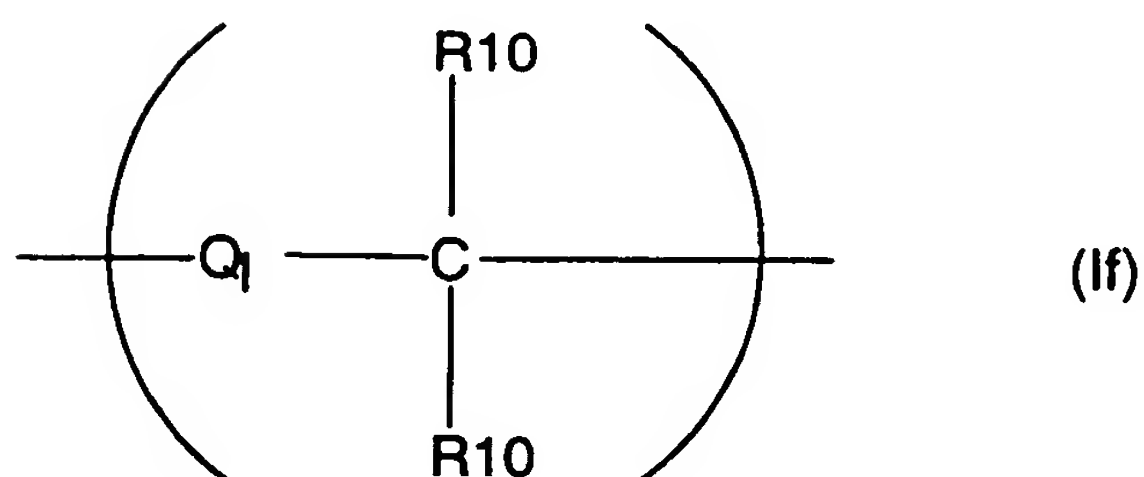
Preferred Subgroups of Compounds of Formula (III):
Preferred R₁ substituents:

A preferred subclass of compounds of formula (III)
 5 are those where for R₁ the divalent linking group -(L₁)-
 is a group represented by any one of the following
 formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



10

or



15 where Q₁ is a bond or any of the divalent groups (Ia),
 (Ib), (Ic), (Id), (Ie), and (If) and each R₁₀ is

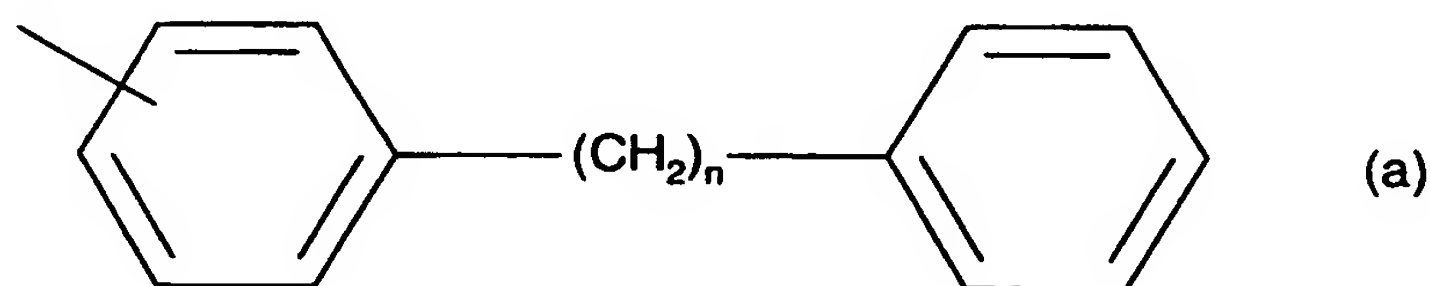
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independently hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl or C₁₋₈ alkoxy.

Particularly preferred as the linking group -(L₁)- of
5 R₁ is an alkylene chain of 1 or 2 carbon atoms, namely,
-(CH₂)- or -(CH₂-CH₂)-.

The preferred group for R₁₁ is a substituted or
unsubstituted group selected from the group consisting of
10 C₅-C₁₄ cycloalkyl, C₅-C₁₄ cycloalkenyl, phenyl, naphthyl,
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
indenyl, stilbenyl, terphenyl, diphenylethylenyl,
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
biphenyl, bibenzylyl and related bibenzylyl homologues
15 represented by the formula (a);

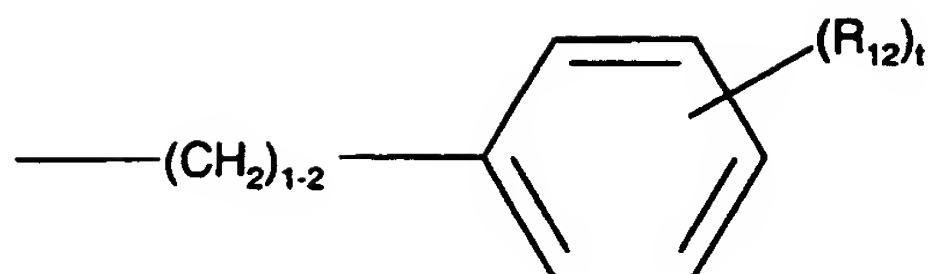


where n is a number from 1 to 8.

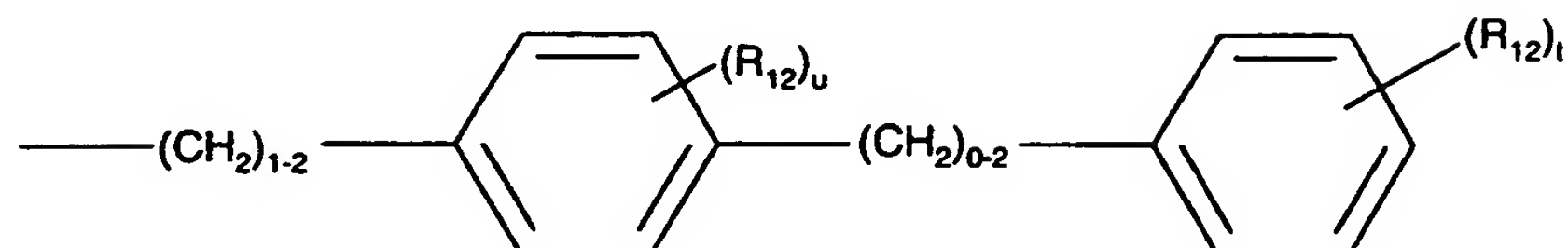
20 Particularly preferred are compounds wherein for R₁
the combined group -(L₁)-R₁₁ is selected from the group
consisting of

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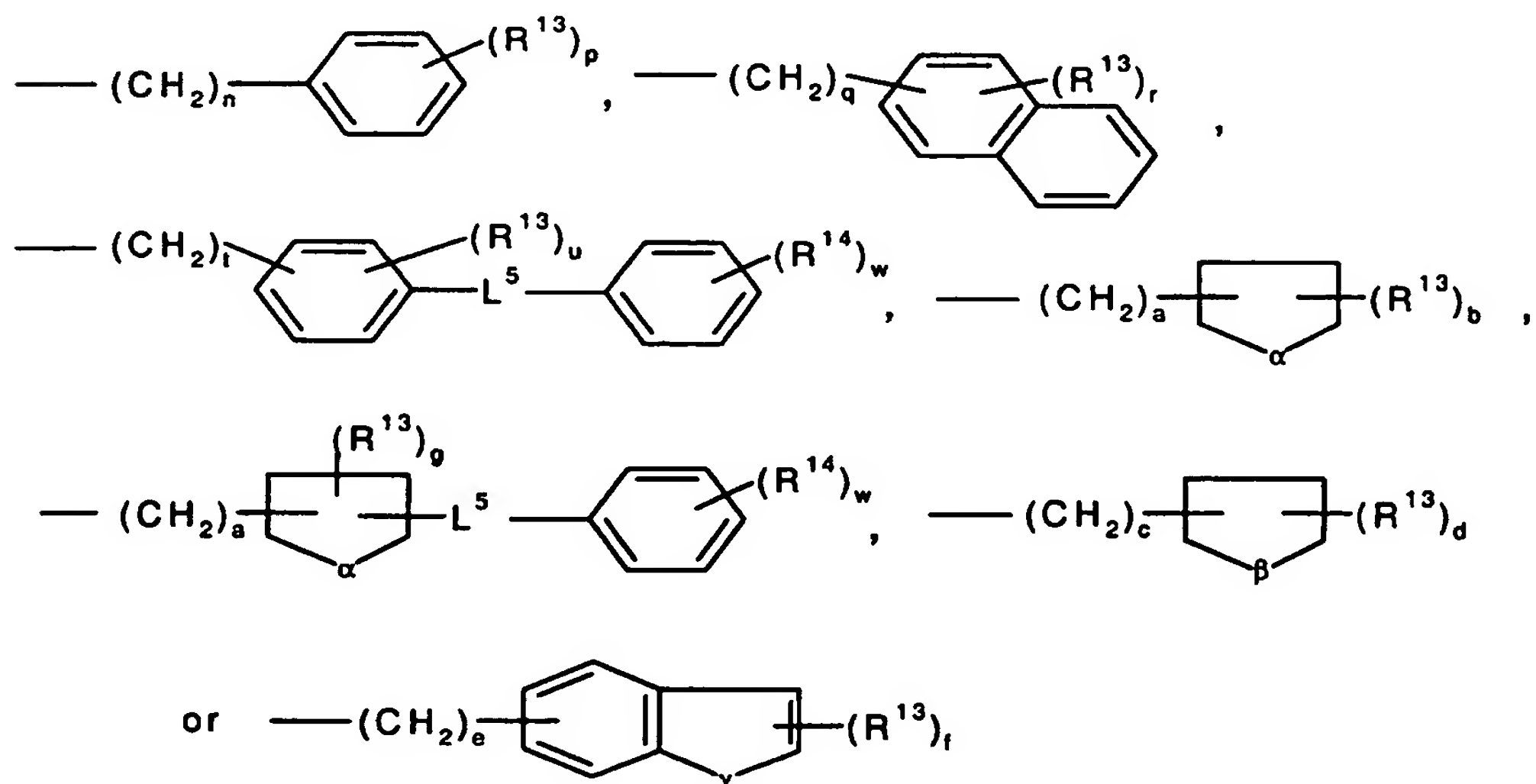


or



where R_{12} is a radical independently selected from halo, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8$
 5 $\text{alkyl})$ and C_1 - C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

Also preferred for R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an
 integer from 1 to 6, and R^{12} is (d) a group represented by
 10 the formula:



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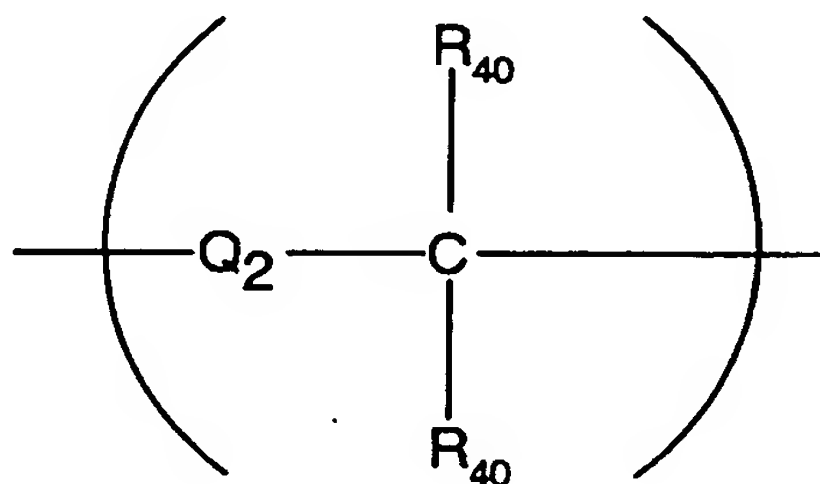
wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl; C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$, $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

Preferred R_2 substituents:

R_2 is preferably selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, $-O-(C_1-C_3$ alkyl), $-S-(C_1-C_3$ alkyl), $-C_3-C_4$ cycloalkyl $-CF_3$, halo, $-NO_2$, $-CN$, $-SO_3$. Particularly preferred R_2 groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-F$, $-CF_3$, $-Cl$, $-Br$, or $-O-CH_3$.

Preferred R₄ substituents:

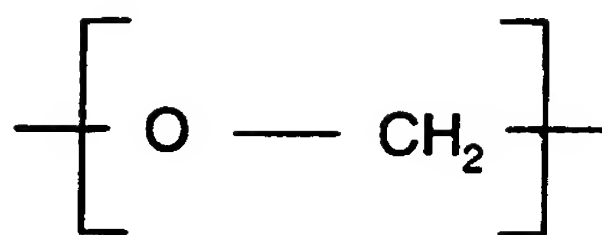
Another preferred subclass of compounds of formula (III) are those wherein R₄ is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, -(L_C)-, for R₄ is selected from a group represented by the formula;



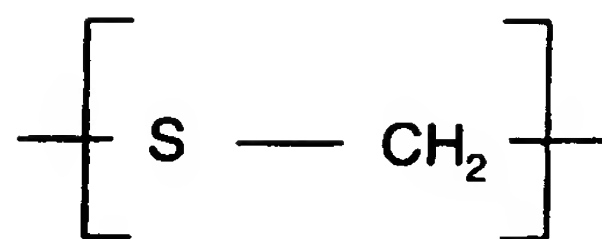
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where Q₂ is selected from the group -(CH₂)-, -O-, -NH-, -C(O)-, and -S-, and each R₄₀ is independently selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, -(L_C)-, for R₄ is selected from the specific groups;

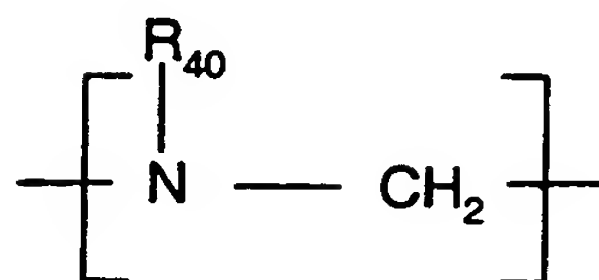
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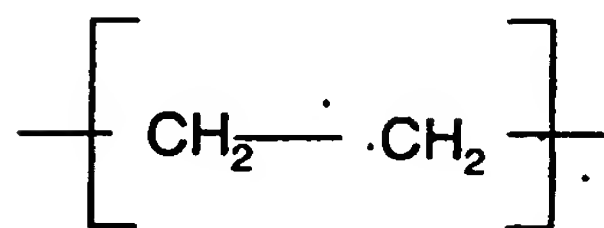
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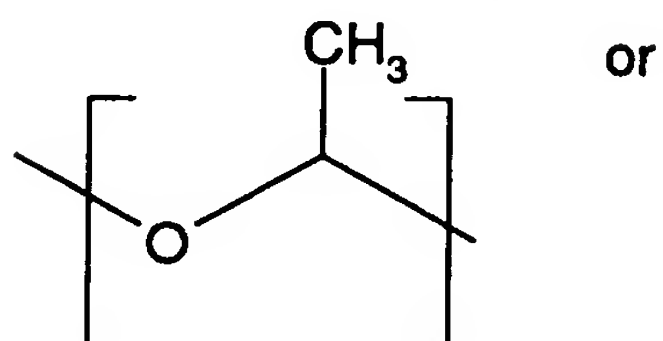
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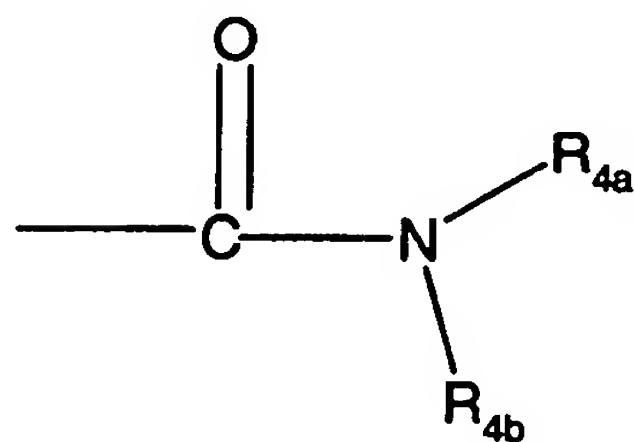


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where R_{40} is hydrogen or C_1 - C_8 alkyl.

Preferred as the (acylamino acid group) in the group R_4

5 is the group:



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wherein R^{4a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof.

A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

Particularly preferred are R^{4b} groups that combine with the nitrogen atom to represent amino acid groups selected from: glycine, glycine methyl ester, L-alanine, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L-valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

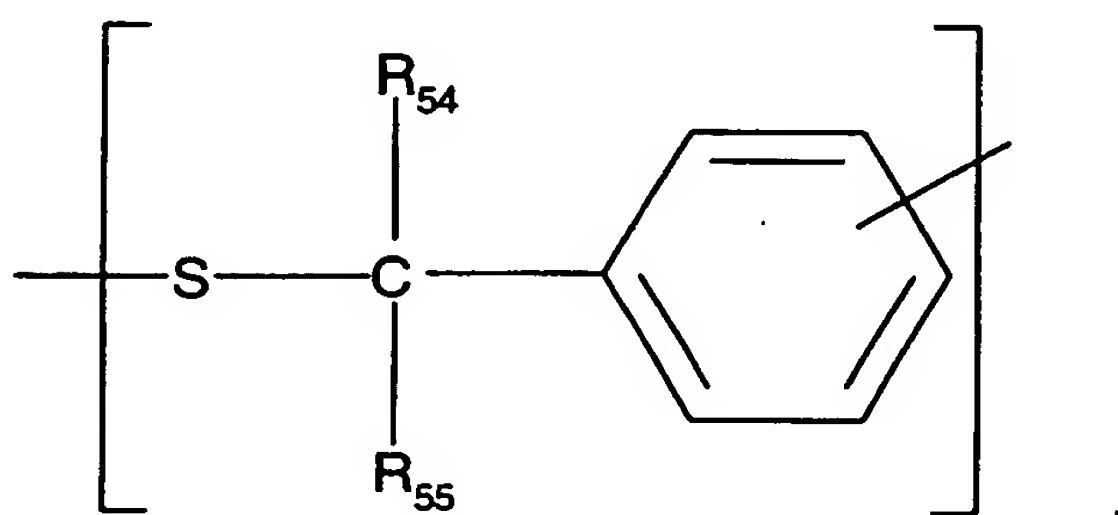
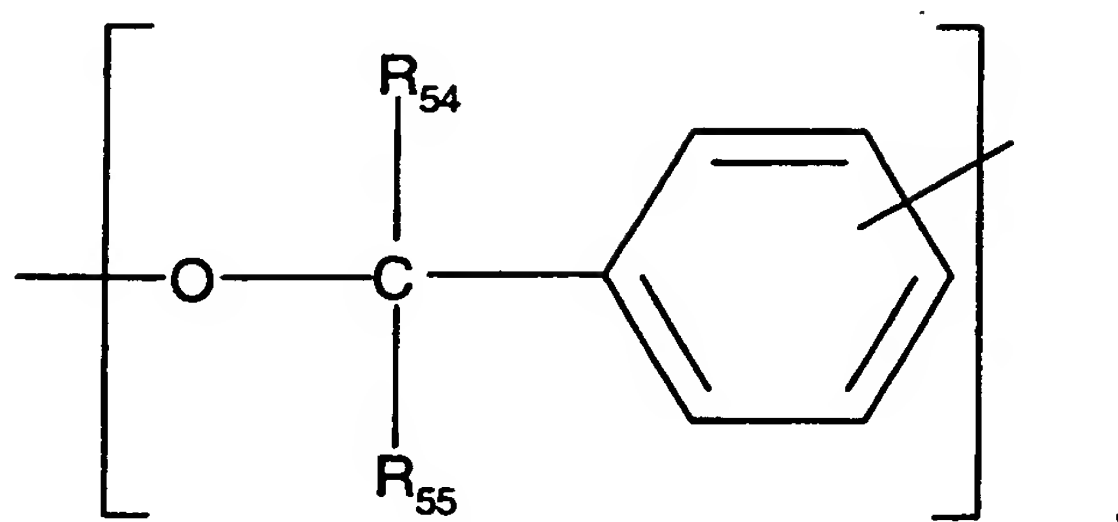
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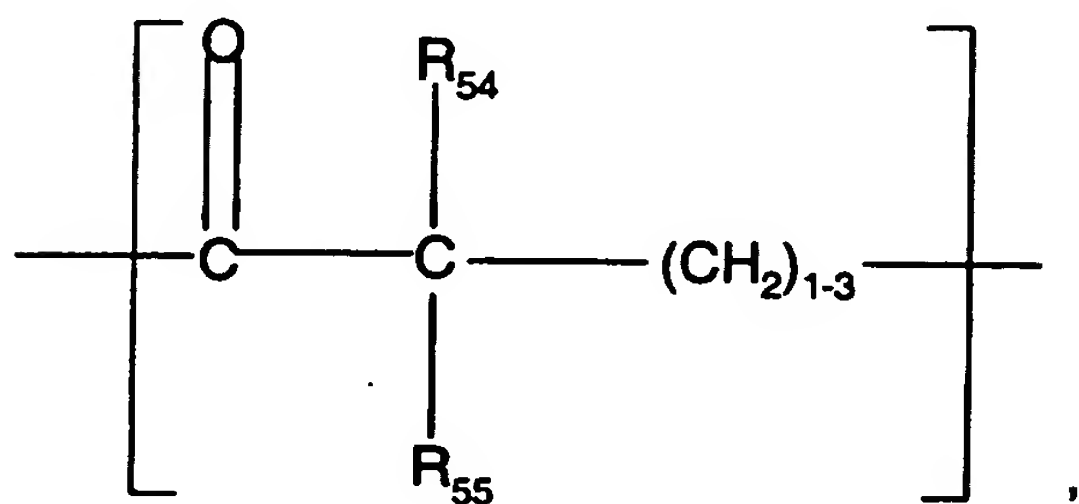
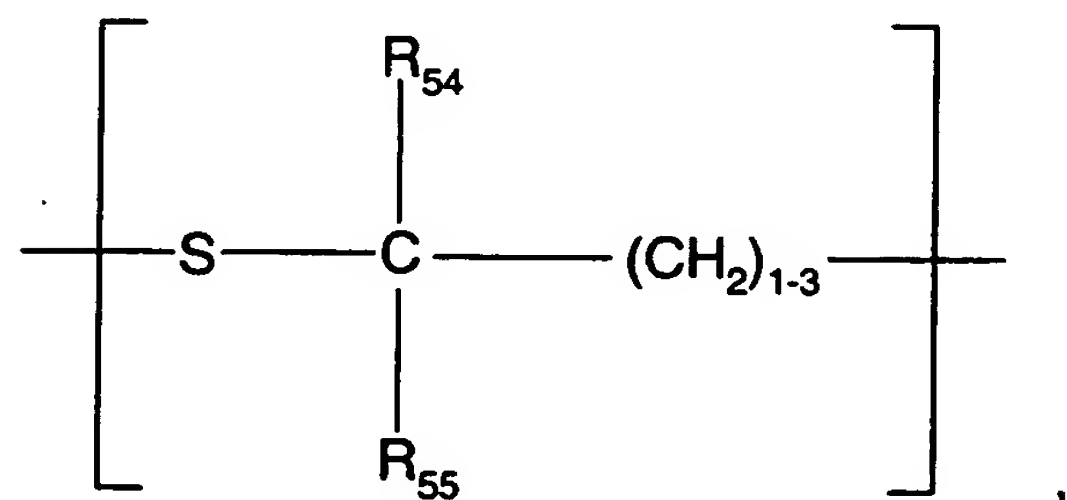
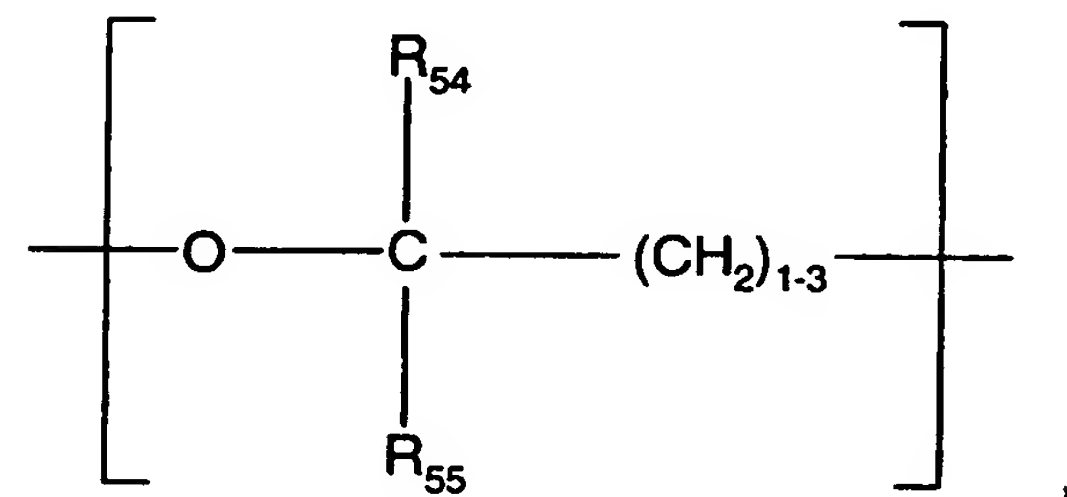
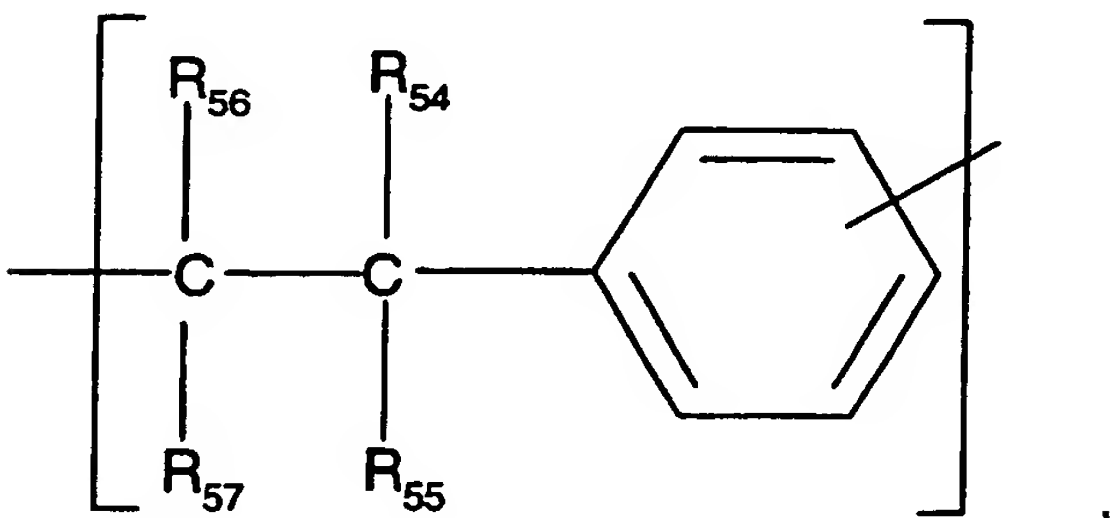
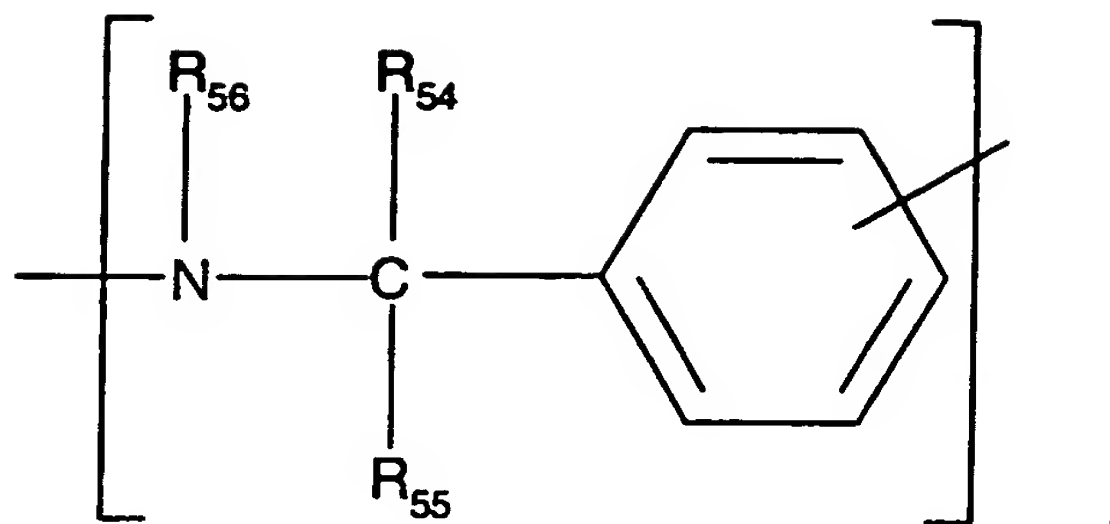
Preferred R₅ Substituents:

Preferred acid linker, $-(L_a)-$, for R₅ is selected from the group consisting of;

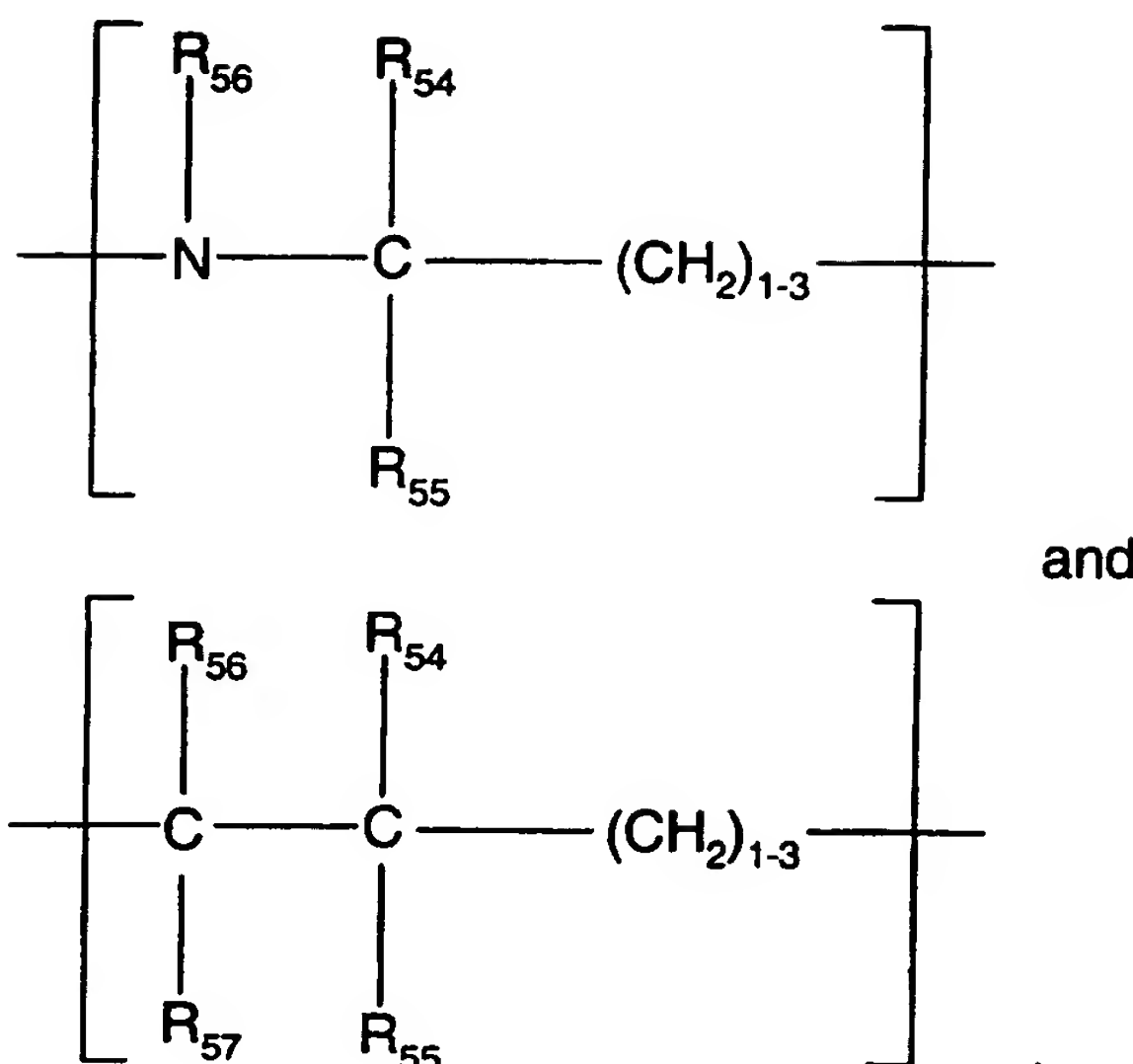
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wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo. Preferred (acidic group) for R₅ is selected from the group consisting of -CO₂H, -SO₃H and -P(O)(OH)₂

Preferred R₆ and R₇ substituents:

Another preferred subclass of compounds of formula (III) are those wherein for R₆ and R₇ the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂

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alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂
alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂
alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio,
C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆
5 alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆
haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl,
-C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy,
phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino,
bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H,
10 chloro, cyano, cyanoguanidinyl, fluoro, guanidino,
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,
iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl,
and carbonyl; where n is from 1 to 8.

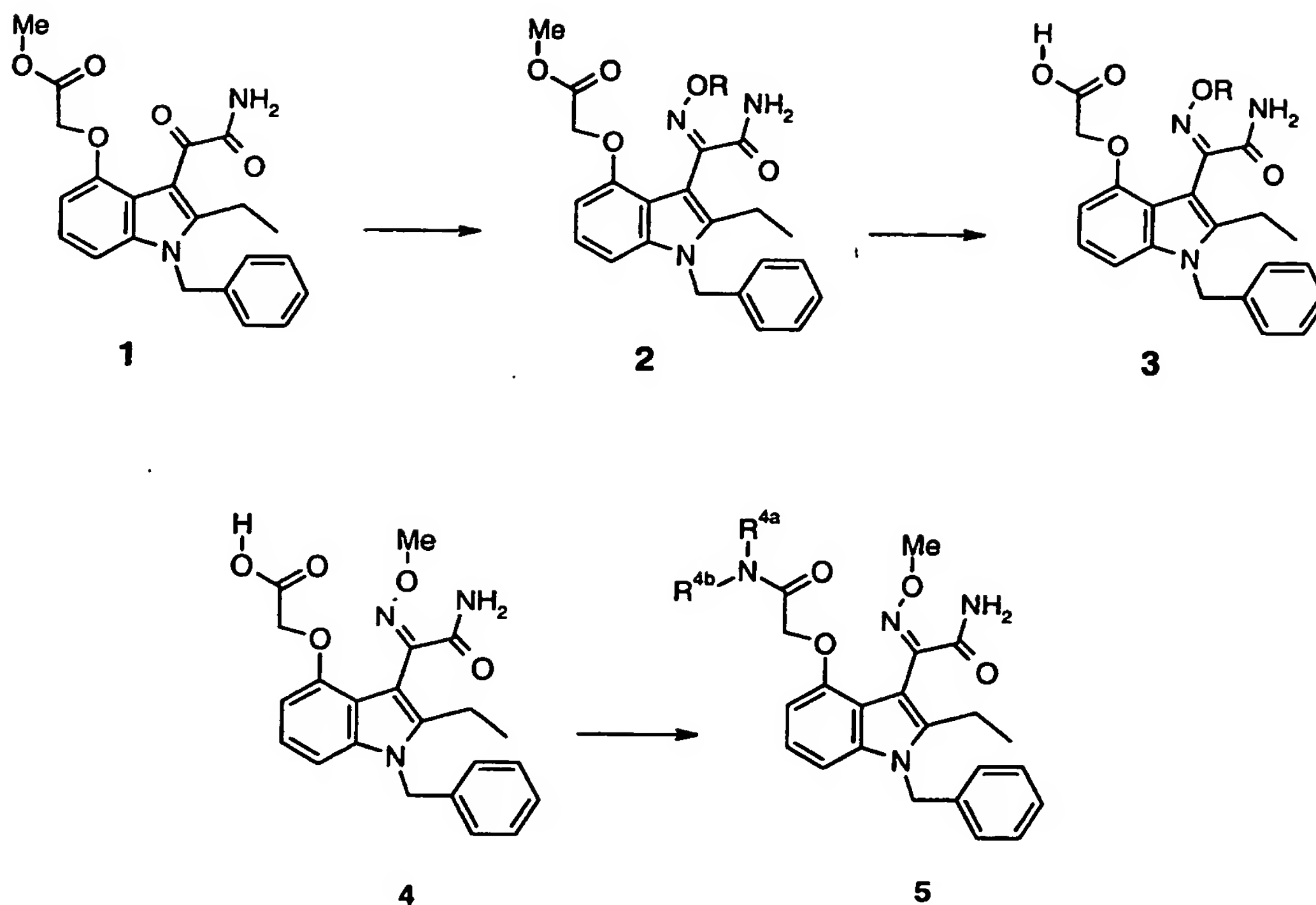
15 Most preferred as non-interfering substituents are
methyl, ethyl, propyl, and isopropyl.

The indole-3-oxime compounds of the invention can be
prepared following protocol of scheme 2 below;

20

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Scheme 2



5

To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in scheme 1, compound 1 in scheme 2, *supra.*) is heated with hydroxylamine hydrochloride (when R is H) in a THF/methanol mixture for 8 hours or until the reaction was deemed complete. The reaction product is isolated by chromatography or other known laboratory procedure to afford a white solid. Substituted oximes such as when R is methyl, ethyl, phenyl or other substituent can be prepared by reacting the corresponding substituted hydroxylamine hydrochloride or free base with the

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glyoxylamide as described *supra*. The ester functionality at the 4 or 5 position on the indole nucleus, as in for example, compound 2, can be: (a) converted to the acid by hydrolysis using lithium hydroxide or other known ester hydrolysis methods to afford compounds of formula 3, or (b) converted to an amide functionality directly or via the acid functionality to afford compounds of formula 4. General procedures for the conversion of organic acids to amino acid are well known to artisans in the field, and have been documented in general reference texts including, for example, J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989.

15

The oxime acid compounds of formula 3 such as the methyloxime compound such as that of formula 4 can be converted to the corresponding amino acid derivative via the methylester by coupling with various amino acids by general coupling procedures known to one skilled in the art. Additional references, or procedures are found in J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985; R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989 and J. Jones Amino Acids and Peptide

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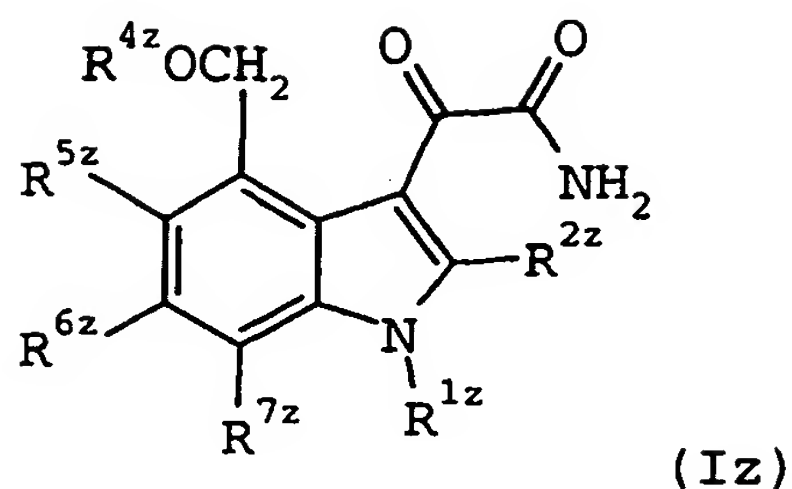
Synthesis, Oxford Science Publications, Stephen G. Davis,
Editor, Oxford University Press Inc., New York, NY, 1992.

5 **III. Method of Making the 1H-Indole-3-Glyoxylamide
Starting Material for Preparing the Compounds of the
Invention:**

 The synthesis of the indole compounds of the
10 invention (viz., Compounds of Formulae I and II) can be
accomplished by well known methods as recorded in the
chemical literature. In particular, the indole starting
materials may be prepared by the synthesis schemes
taught in US Patent No. 5,654,326; the disclosure of
15 which is incorporated herein by reference. Another
method of making 1H-indole-3-glyoxylamide SPLA_2
inhibitors is described in United States Patent
Application Serial No. 09/105381, filed June 26, 1998
and titled, "Process for Preparing 4-substituted 1-H-
20 Indole-3-glyoxyamides" the entire disclosure of which is
incorporated herein by reference.

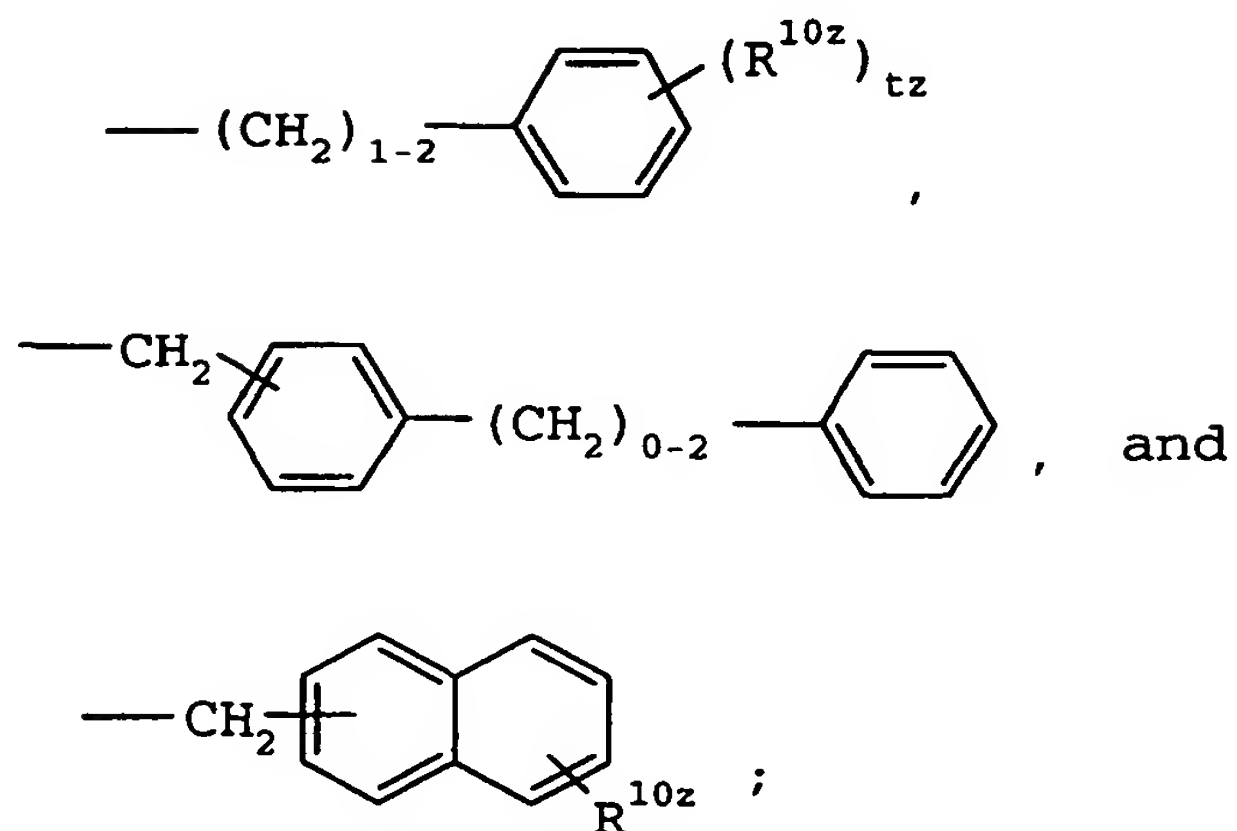
 United States Patent Application Serial
No. 09/105381 discloses the following process having
25 steps (a) thru (i):
Preparing a compound of the formula (Iz) or a
pharmaceutically acceptable salt or prodrug derivative
thereof

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5 wherein:

R^{1z} is selected from the group consisting of -C₇-C₂₀ alkyl,



where

10 R^{10z} is selected from the group consisting of halo, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, -S-(C₁-C₁₀ alkyl) and halo(C₁-C₁₀)alkyl, and tz is an integer from 0 to 5 both inclusive;

15 R^{2z} is selected from the group consisting of hydrogen, halo, C₁-C₃ alkyl, C₃-C₄ cycloalkyl, C₃-C₄

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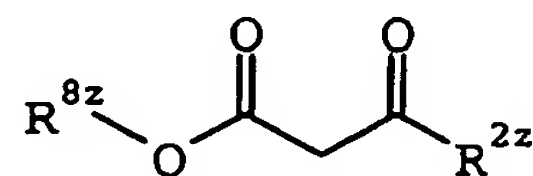
cycloalkenyl, -O-(C₁-C₂ alkyl), -S-(C₁-C₂ alkyl), aryl, aryloxy and HET;

R^{4z} is the group -CO₂H, or salt and prodrug derivative thereof; and

5 R^{5z}, R^{6z} and R^{7z} are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy, halo(C₂-C₆)alkyl, bromo, chloro, fluoro, iodo and aryl;

which process comprises the steps of:

10 a) halogenating a compound of formula Xz

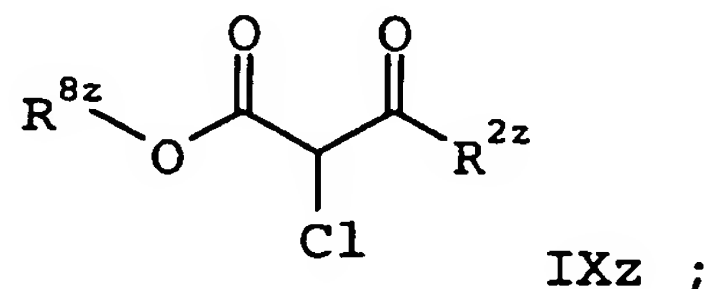


Xz

where R^{8z} is (C₁-C₆)alkyl, aryl or HET;

with SO₂Cl₂ to form a compound of formula

15 IX

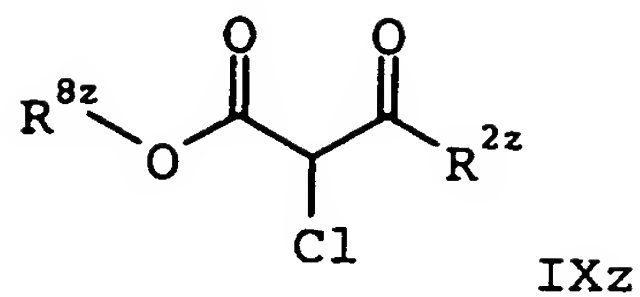


IXz ;

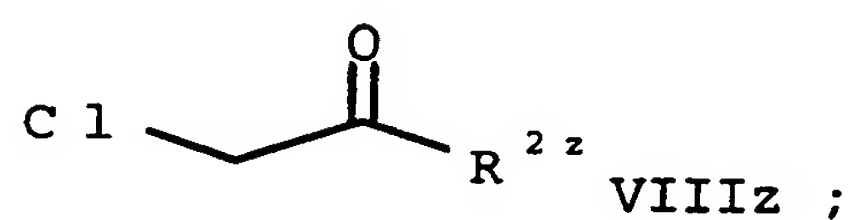
b) hydrolyzing and decarboxylating a compound of formula IXz

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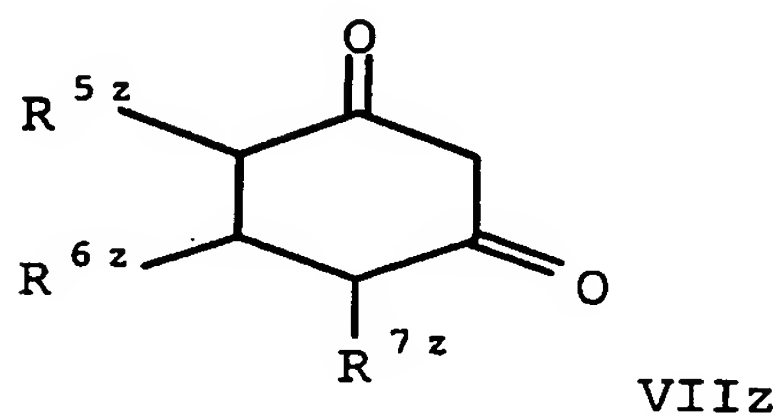
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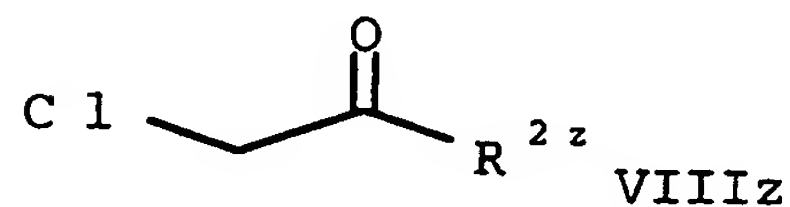
to form a compound of formula VIIIz



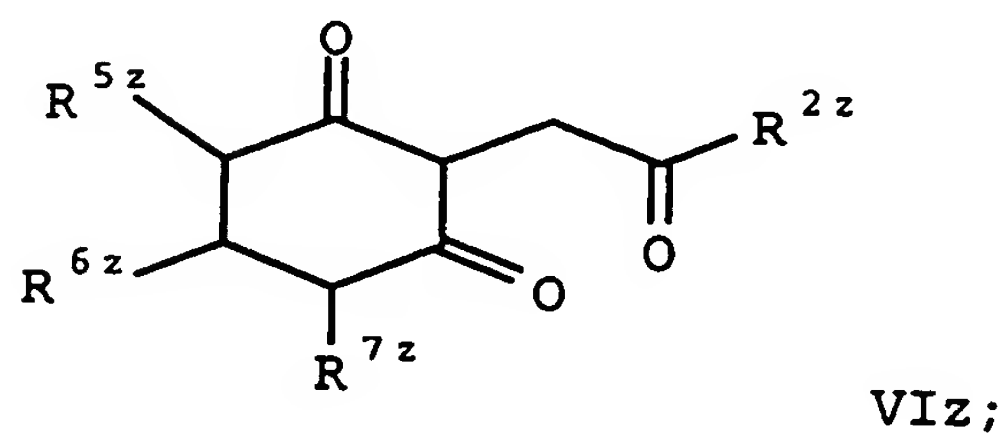
c) alkylating a compound of formula VIIz



with a compound of formula VIIIz



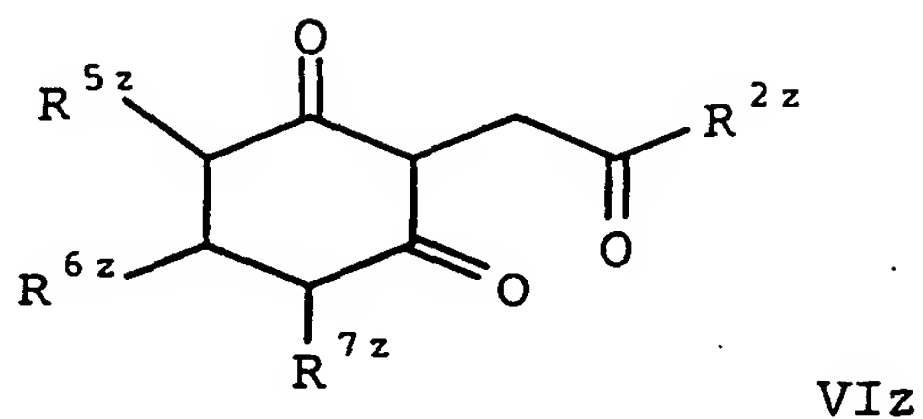
to form a compound of formula VIz



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- d) aminating and dehydrating a compound of formula VIz

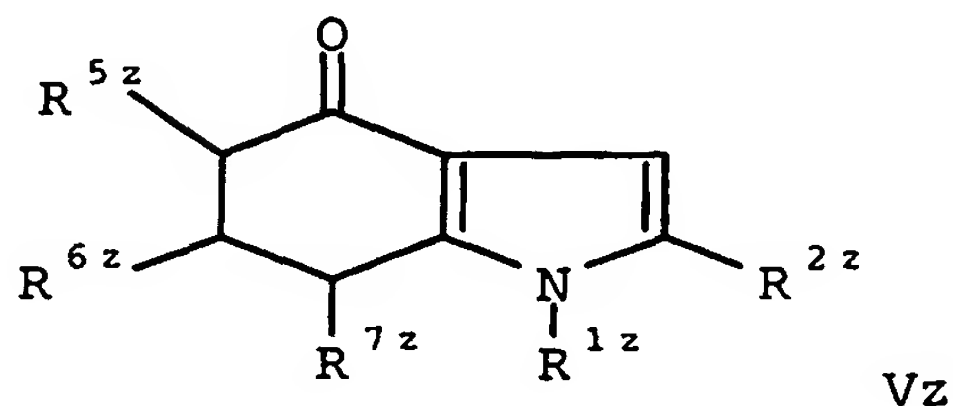


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with an amine of the formula $R^{1z}NH_2$ in the presence of a solvent that forms an azeotrope with water to form a compound of formula Vz;

10

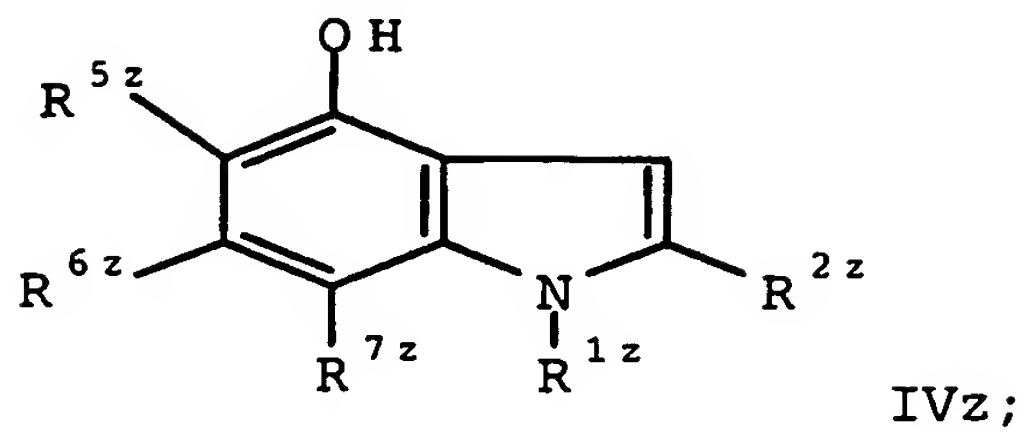
- e) oxidizing a compound of formula Vz



15

by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IVz

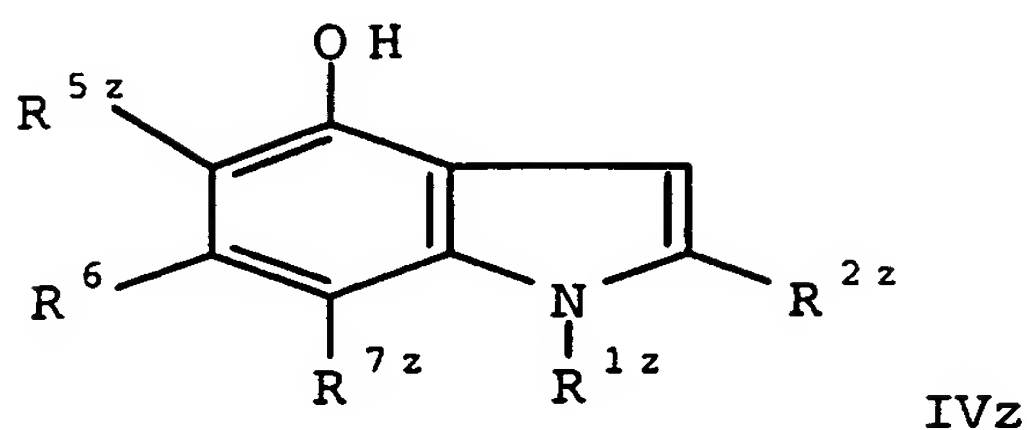
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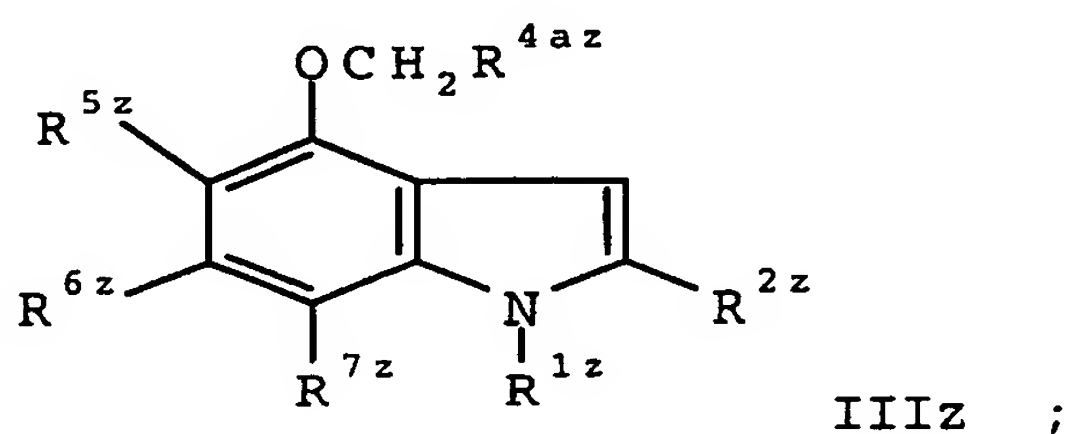
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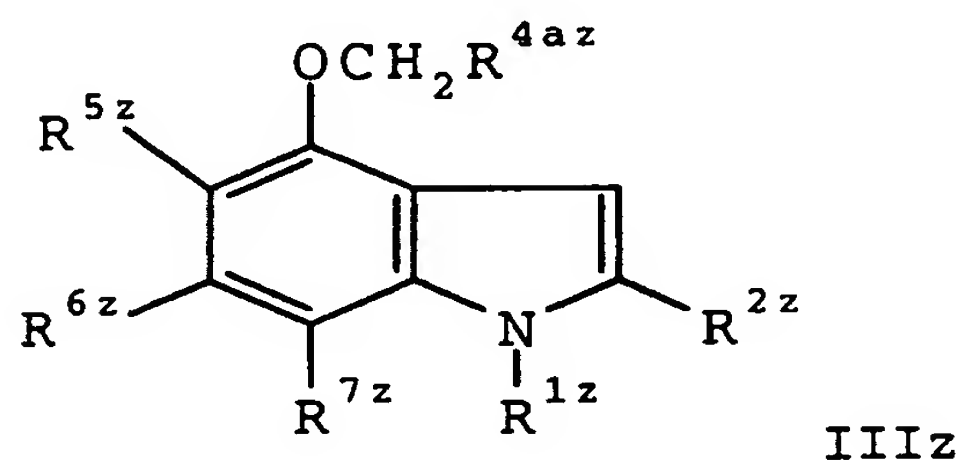
f) alkylating a compound of the formula IVz



with an alkylating agent of the formula XCH_2R^{4az}
 where X is a leaving group and R^{4az} is $-CO_2R^{4b}$,
 where R^{4bz} is an acid protecting group to form a
 compound of formula IIIz

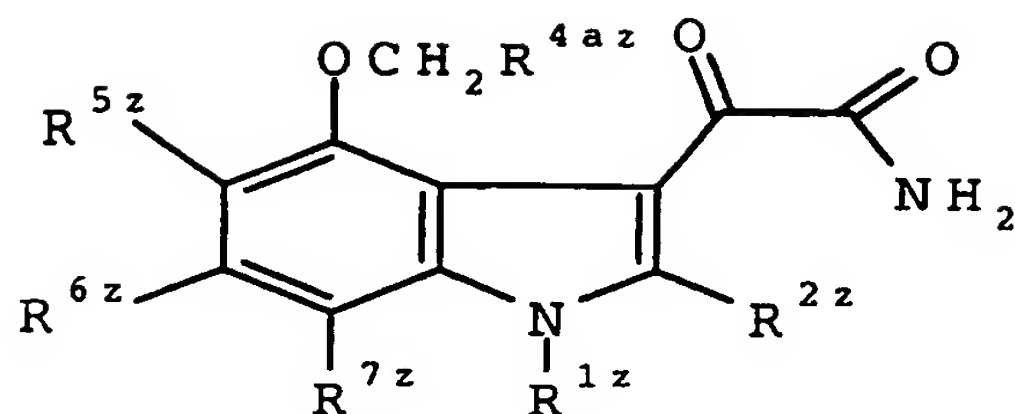


g) reacting a compound of formula IIIz



with oxalyl chloride and ammonia to form a
 compound of formula IIz

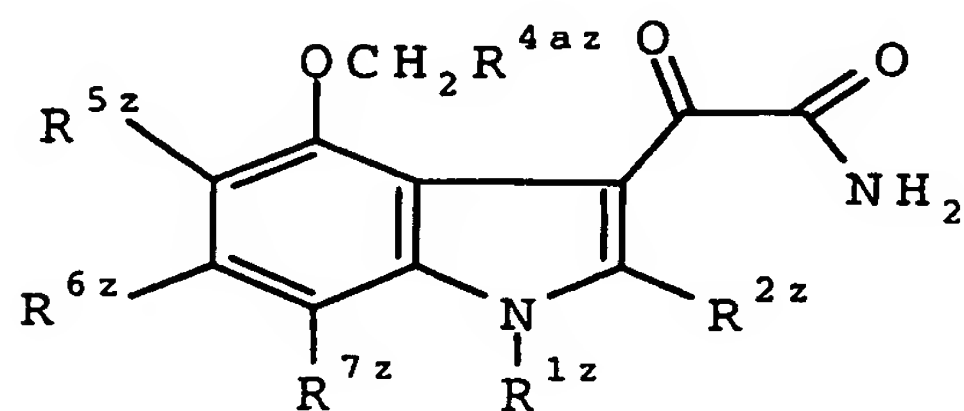
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IIz; and

5

- h) optionally hydrolyzing a compound of formula IIz



10

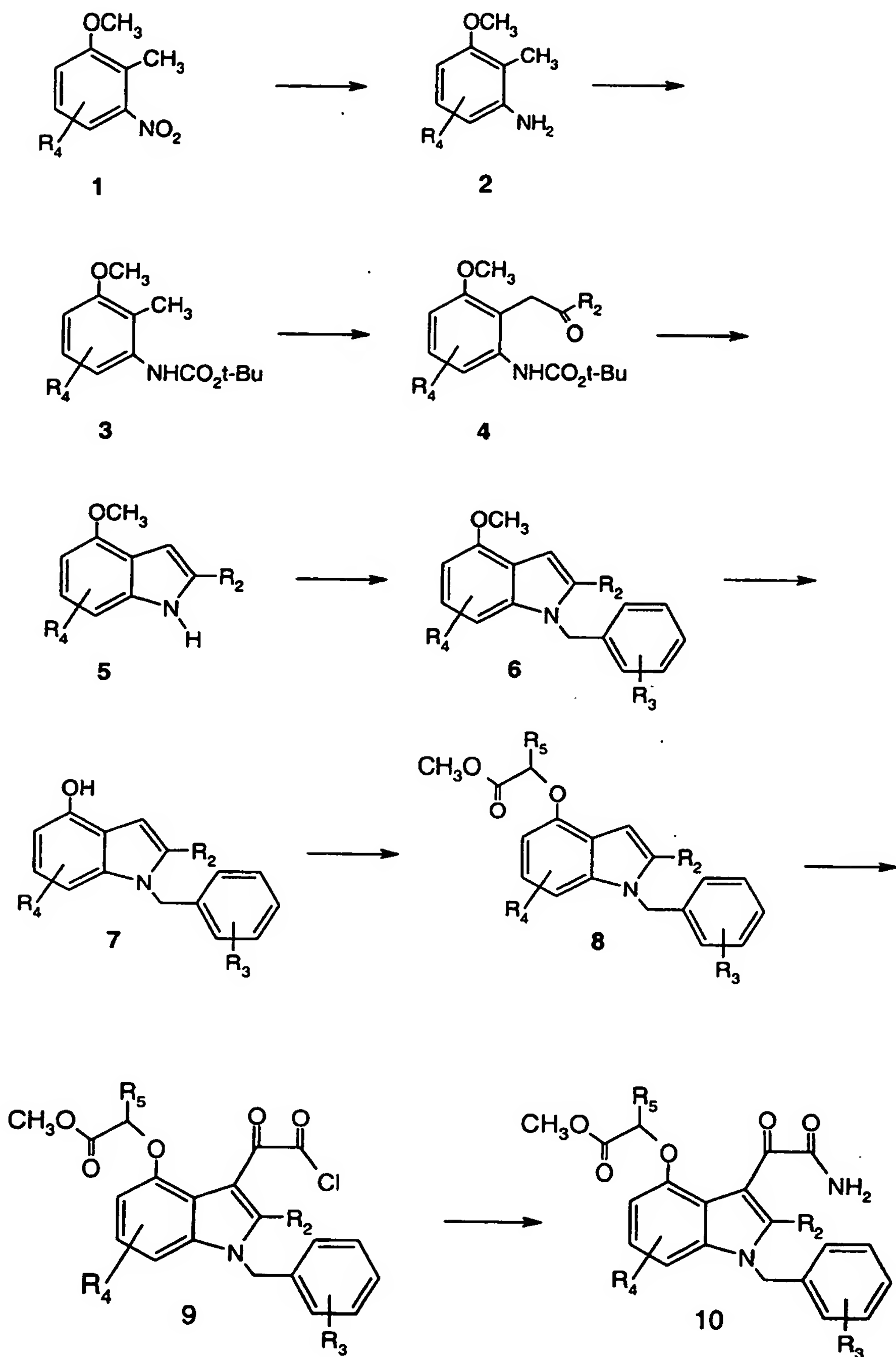
IIz

to form a compound of formula Iz.

An alternative protocol useful for the synthesis of the starting material is shown in Scheme 1 below:

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Scheme 1



5 The synthesis of indole-3-oxime amides (compound of formula I and II, supra.) of this invention uses

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as starting material the glyoxamide ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid methyl ester, compound 10, *supra*. This starting material is prepared as set out in the preceding section or by the method of Example 9 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference).

To obtain the glyoxylamide starting material substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-methoxyaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline 2, obtained, is converted to the N-tert-butyloxycarbonyl derivative 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is

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generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using sodiumhydride as a base, with reaction condition of 5 to 6. The α -[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10.

Glyoxamide starting material compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is incorporated herein by reference.

IV. Methods of Using the Compounds of the Invention:

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) sPLA₂, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting sPLA₂ mediated release of fatty acids comprises contacting mammalian sPLA₂ with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress

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syndrome, pancreatitis, trauma, bronchial asthma,
allergic rhinitis, rheumatoid arthritis, osteoarthritis,
and related diseases which comprises administering to a
mammal (including a human) a therapeutically effective
5 dose of the indole compound of the invention (see,
formulae I and II).

As previously noted the compounds of this invention
are useful for inhibiting sPLA₂ mediated release of
10 fatty acids such as arachidonic acid. By the term,
"inhibiting" is meant the prevention or therapeutically
significant reduction in release of sPLA₂ initiated
fatty acids by the compounds of the invention. By
"pharmaceutically acceptable" it is meant the carrier,
15 diluent or excipient must be compatible with the other
ingredients of the formulation and not deleterious to
the recipient thereof.

The specific dose of a compound administered
20 according to this invention to obtain therapeutic or
prophylactic effects will, of course, be determined by the
particular circumstances surrounding the case, including,
for example, the compound administered, the route of
administration and the condition being treated. Typical
25 daily doses will contain a non-toxic dosage level of from

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about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical

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formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound.

The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also

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act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

5 Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or
10 acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

 In powders the carrier is a finely divided solid which is in admixture with the finely divided Active
15 ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active
20 ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa
25 butter.

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Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

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Formulation 2

A tablet is prepared using the ingredients below:

	<u>Quantity (mg/tablet)</u>
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

10 An aerosol solution is prepared containing the following components:

	<u>Weight</u>
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

15 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and

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diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

- 5 Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

- 10 The Active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and
- 15 passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each
- 20 weighing 150 mg.

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Formulation 5

Capsules, each containing 80 mg of Active ingredient,
are made as follows:

5

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The Active ingredient, cellulose, starch, and
magnesium stearate are blended, passed through a No. 45
mesh U.S. sieve, and filled into hard gelatin capsules in
10 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active
ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

15

The Active ingredient is passed through a No. 60 mesh
U.S. sieve and suspended in the saturated fatty acid
glycerides previously melted using the minimum heat
necessary. The mixture is then poured into a suppository
20 mold of nominal 2 g capacity and allowed to cool.

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Formulation 7

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

5

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

10

Formulation 8

An intravenous formulation may be prepared as follows:

15

Active ingredient	100 mg
Isotonic saline	1,000 ml

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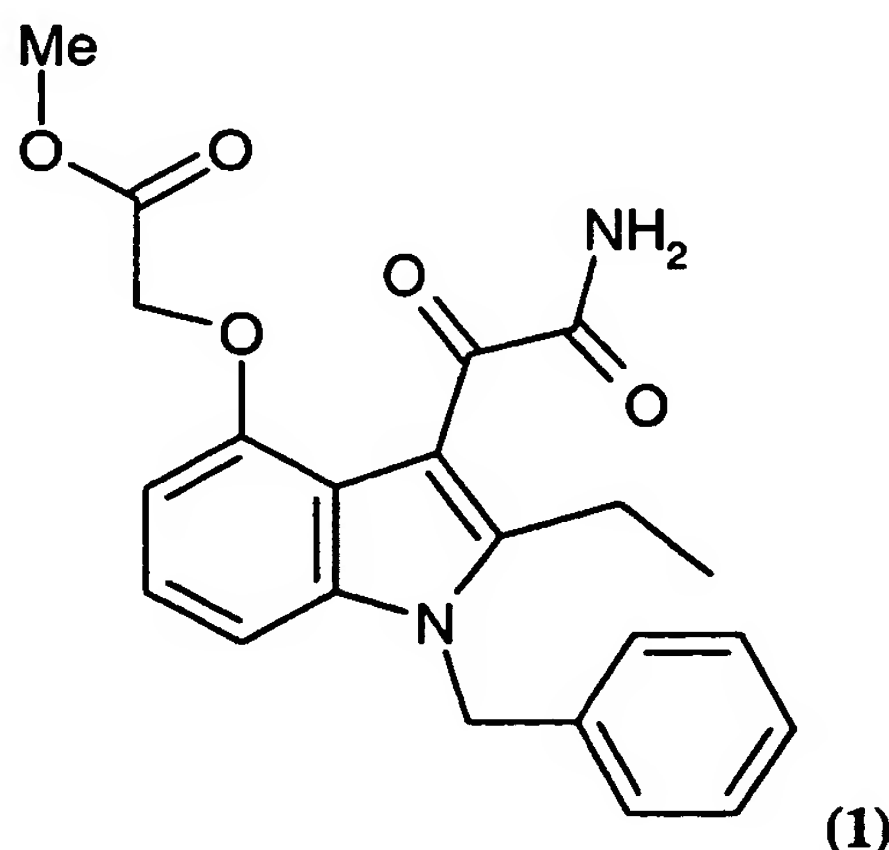
The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

5 All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

10

Example 1

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, a compound represented by the compound of formula (1) formula:



15

Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol)

20

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in 250 mL of THF keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0°C and then the bath replaced. After the temperature had cooled to -60°C ,
5 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl.
10 The organic layer was separated, washed with water, brine, dried over MgSO_4 , and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of
15 trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried (MgSO_4) and concentrated. The residue was chromatographed three
20 times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for $\text{C}_{11}\text{H}_{13}\text{NO}$:

Calculated: C, 75.40; H, 7.48; N, 7.99

Found: C, 74.41; H, 7.64; N, 7.97.

25

Part B. Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

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2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL (24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried (MgSO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.

3.1g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M BBr_3 in methylene chloride with stirring at room temperature for 5 hours, followed by concentration at reduced pressure. The residue was dissolved in ethyl acetate, washed with brine and dried (MgSO_4). After concentrating at reduced pressure, the residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.58g (54% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90°C.

Analyses for $\text{C}_{17}\text{H}_{17}\text{NO}$:

Calculated: C, 81.24; H, 6.82; N, 5.57
Found: C, 81.08; H, 6.92; N, 5.41.

Part D. Preparation of [[2-Ethyl-1-(phenylmethyl)-

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1H-indol-4-yl]oxy]ac tic acid methyl ster.

2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56g, 6.2 mmol) was added to a mixture of 248mg (6.2 mmol) of 60% NaH/mineral oil in 20mL DMF and stirred for 0.67 hour.

5

Then 0.6 mL(6.2 mmol) of methyl bromoacetate was added and stirring was continued for 17 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with
10 brine, dried (MgSO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane, to give 1.37g (69% yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 89-92°C.

15 Analyses for $\text{C}_{20}\text{H}_{21}\text{NO}_3$:

Calculated: C, 74.28; H, 6.55; N, 4.33

Found: C, 74.03; H, 6.49; N, 4.60.

20 **Part E. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.**

Oxalyl chloride (0.4 mL, 4.2 mmol) was added to 1.36g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester in 10 mL of methylene
25 chloride and the mixture stirred for 1.5 hours. The mixture was concentrated at reduced pressure and residue taken up in 10 mL of methylene chloride. Anhydrous ammonia was bubbled in for 0.25 hours, the mixture stirred

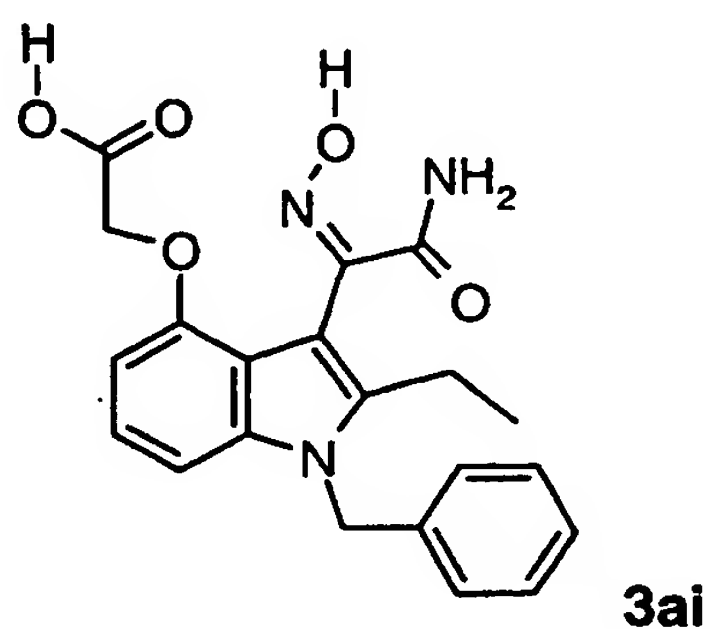
-88-

for 1.5 hours and evaporated at reduced pressure. The residue was stirred with 20 mL of ethyl acetate and the mixture filtered. The filtrate was concentrated to give 1.37g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187°C.

Example 2

10 (indol-3-oxime amide starting material)

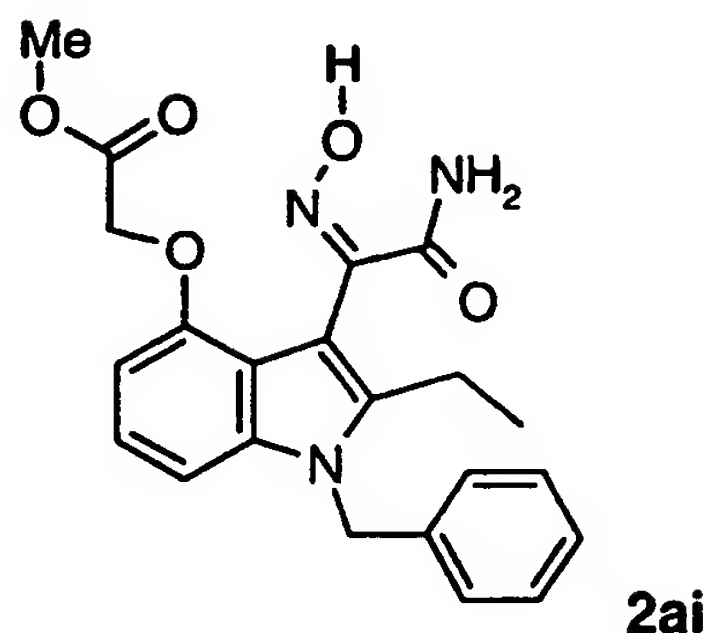
2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.



A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

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A stirred mixture of **1** (600 mg, 1.52 mmol) and hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH₃OH (4 mL) was heated at 55 °C for 8 h. After concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH₂Cl₂) to give the title compound **2ai** (285 mg) as a white solid in 46% yield. IR (CHCl₃) 3510, 3415, 1757, 1667 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.84 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.98-7.07 (m, 3H), 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (*M*⁺+1).

Elemental Analyses for C₂₂H₂₃N₃O₅·0.30(H₂O):

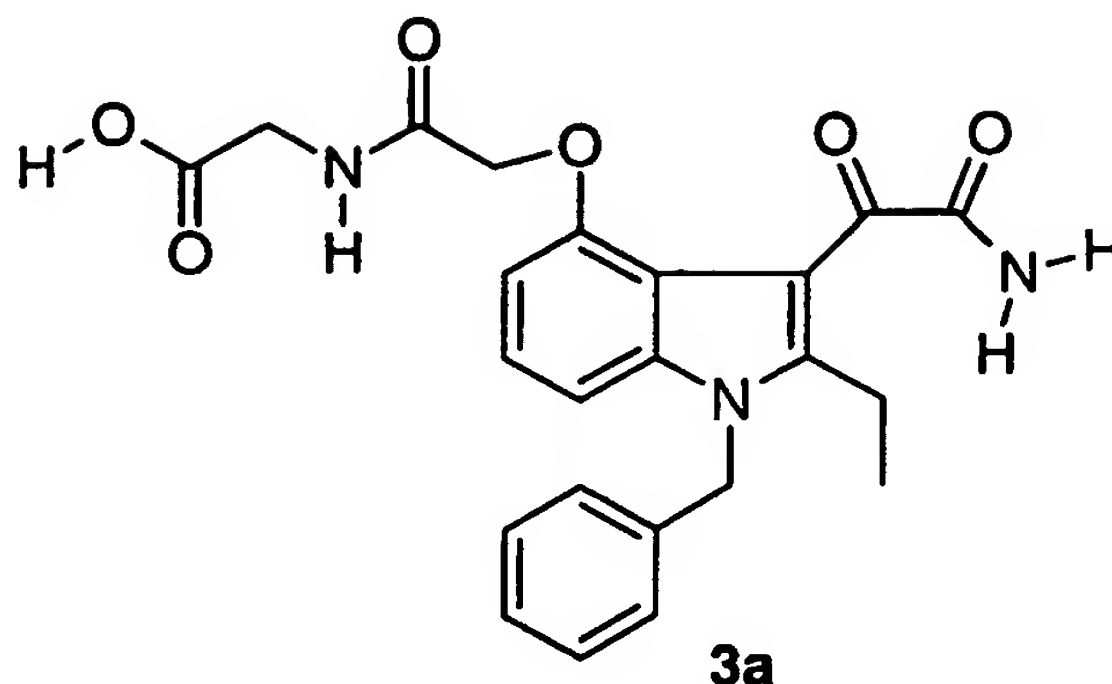
Calculated: C, 63.70; H, 5.73; N, 10.13;
Found: C, 63.68; H, 5.62; N, 10.20.

Example 3

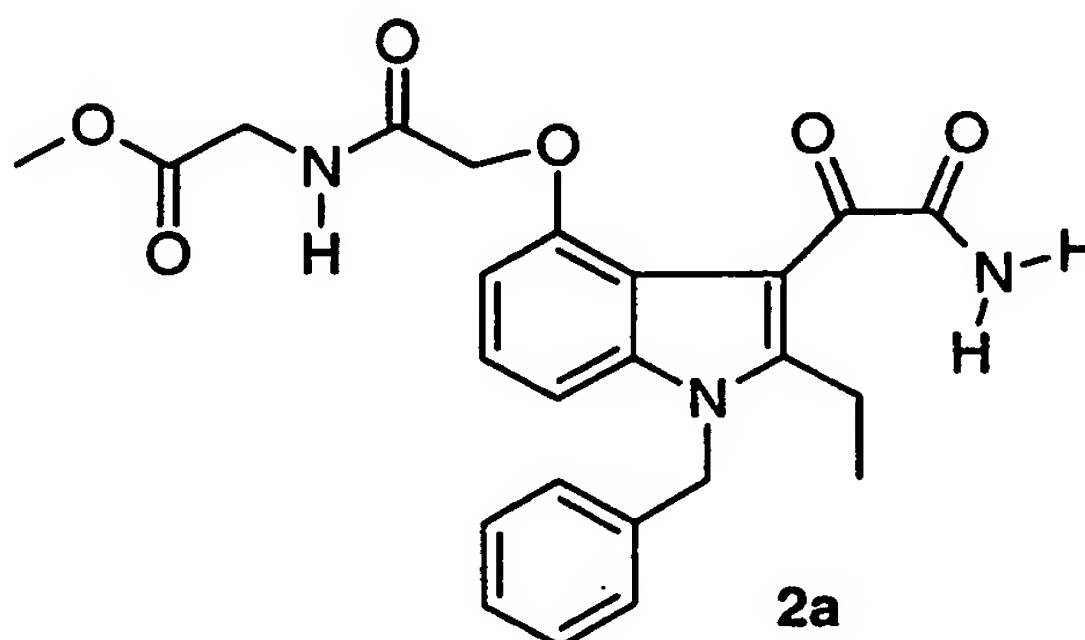
N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]glycine

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A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester



5

To a solution of **1** (0.100 g, 0.249 mmol) in 2 mL DMF was added collidine (0.069 mL, 0.523 mmol), methyl glycine hydrochloride (0.0313 g, 0.249 mmol), and benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.115 g, 0.261) sequentially at room temperature. After 2.5 hrs. the reaction mixture was concentrated in vacuo to near dryness, then it was taken up in CH₂Cl₂, chromatographed on a silica gel column (gradient 20-40% THF in CH₂Cl₂) and dried in an 80°C vacuum oven to give 0.0768 g of **2a** as a yellow solid in 68% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 6.8 Hz, 3H), 2.90 (br q, J = 6.8 Hz, 2H),

10

15

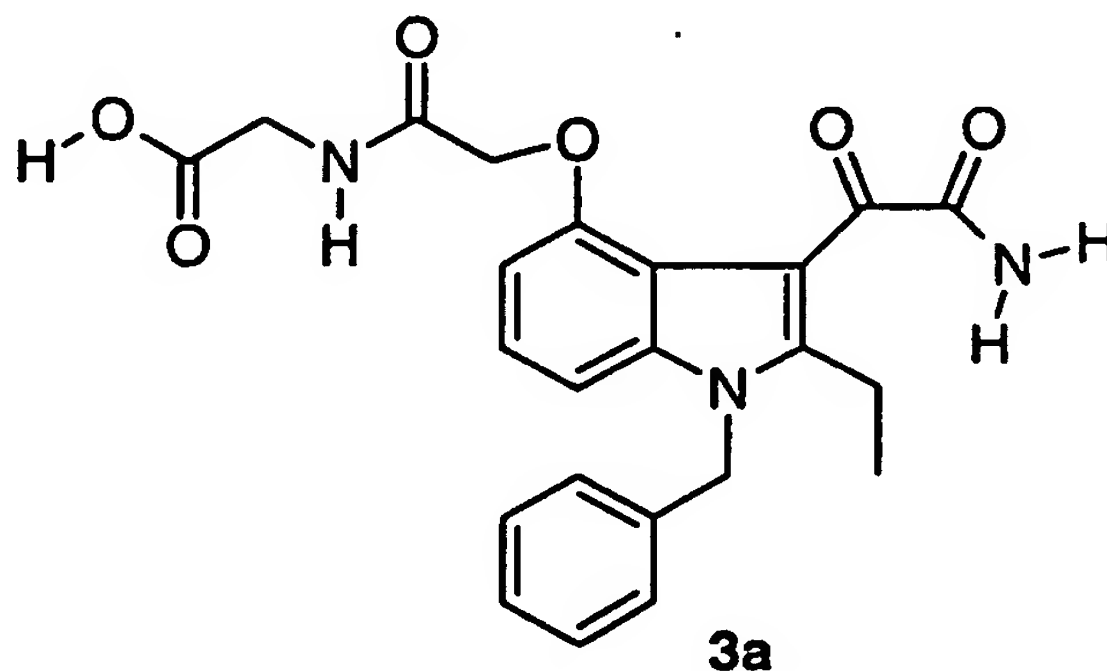
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3.57 (s, 3H), 3.88 (d, $J = 5.5$ Hz, 2H), 4.57 (s, 2H), 5.51 (s, 2H), 6.59 (d, $J = 5.6$ Hz, 1H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t, $J = 5.5$ Hz, 1H).

5

B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine



10 To a solution of 2a (0.035 g, 0.078 mmol) in 1 mL THF, 1 mL MeOH and 0.25 mL distilled H₂O was added 4.17N LiOH (0.093 mL, 0.388 mmol) at room temperature. After 2 hrs. the reaction mixture was acidified with 5N HCl (0.093 mL, 0.465 mmol) and concentrated *in vacuo*. The residue
15 was taken up in CH₂Cl₂, then rapidly triturated with hexanes to give a yellow suspension which was filtered and dried in an 80°C vacuum oven to give 0.0336 g of 3a as a yellow solid in 99% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, $J = 5.9$ Hz, 3H), 2.90 (br q, $J = 5.9$ Hz, 2H), 3.80 (d, $J = 4.8$ Hz, 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, $J = 5.8$ Hz, 1H),
20 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, $J = 5.8$ Hz, 1H),

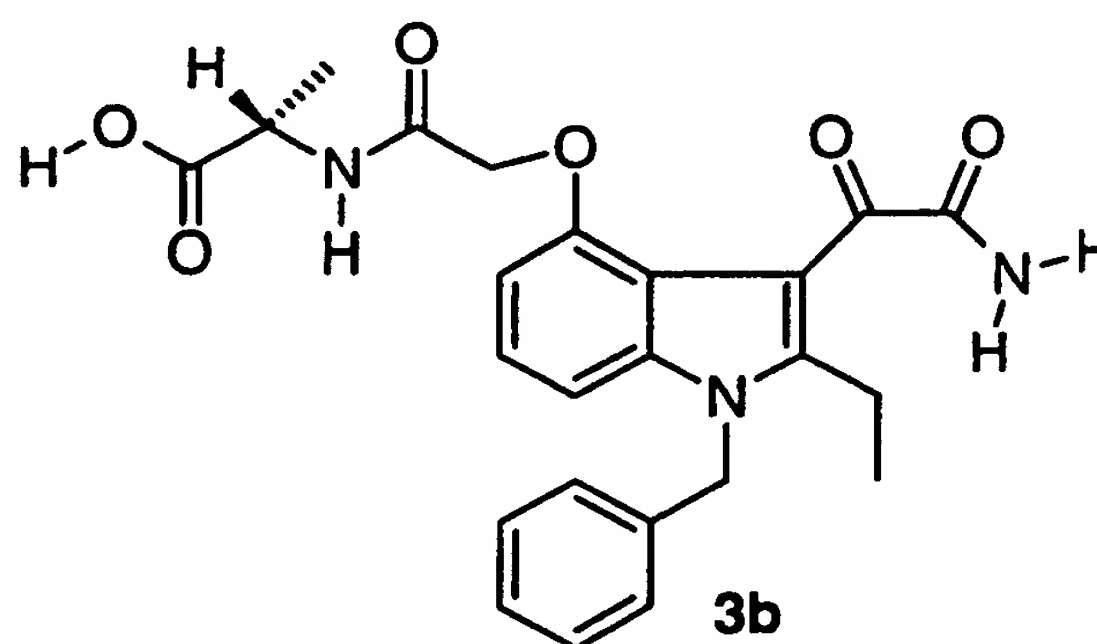
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7.01-7.28 (m, 7H), 7.54 (s, 1H), 7.99 (s, 1H), 8.31 (t, J = 4.8 Hz, 1H), 12.25-12.75 (br s, 1H).

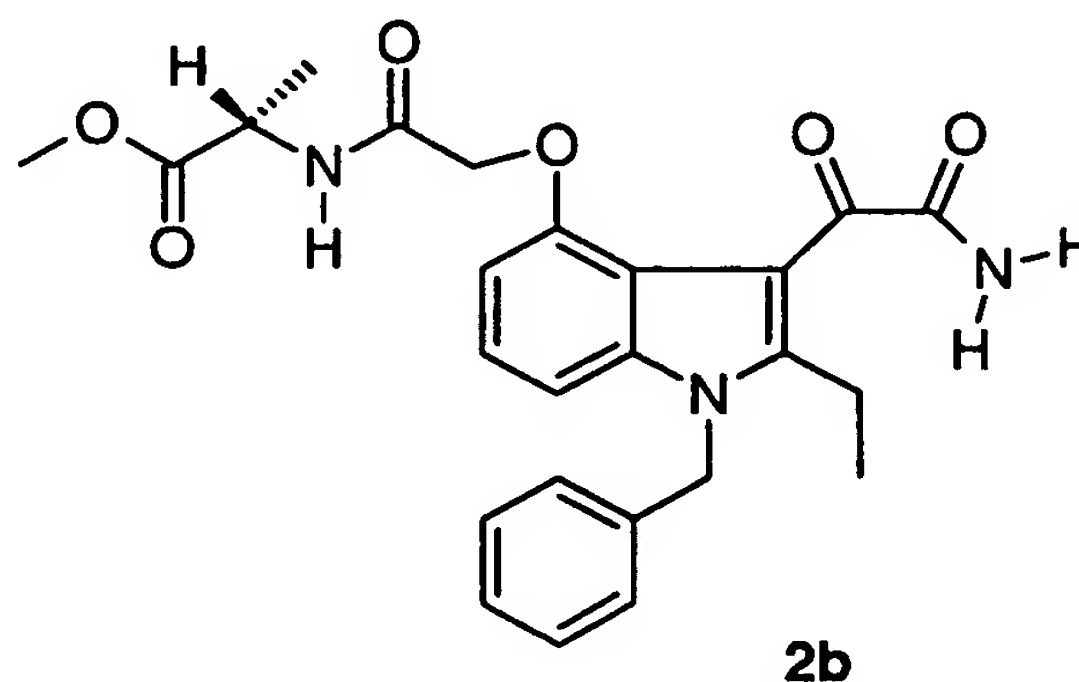
Example 4

5 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine



A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester

10



Following the experimental procedure as described for 2a, 2b was obtained as a yellow solid in 65% yield.

^1H NMR (DMSO- d_6) δ 1.04 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 7.3 Hz, 3H), 2.91 (br q, J = 7.2 Hz, 2H), 3.54 (s, 3H), 4.29 (qd, J = 7.3, 6.8 Hz, 1H), 4.55 (s, 2H), 5.51 (s,

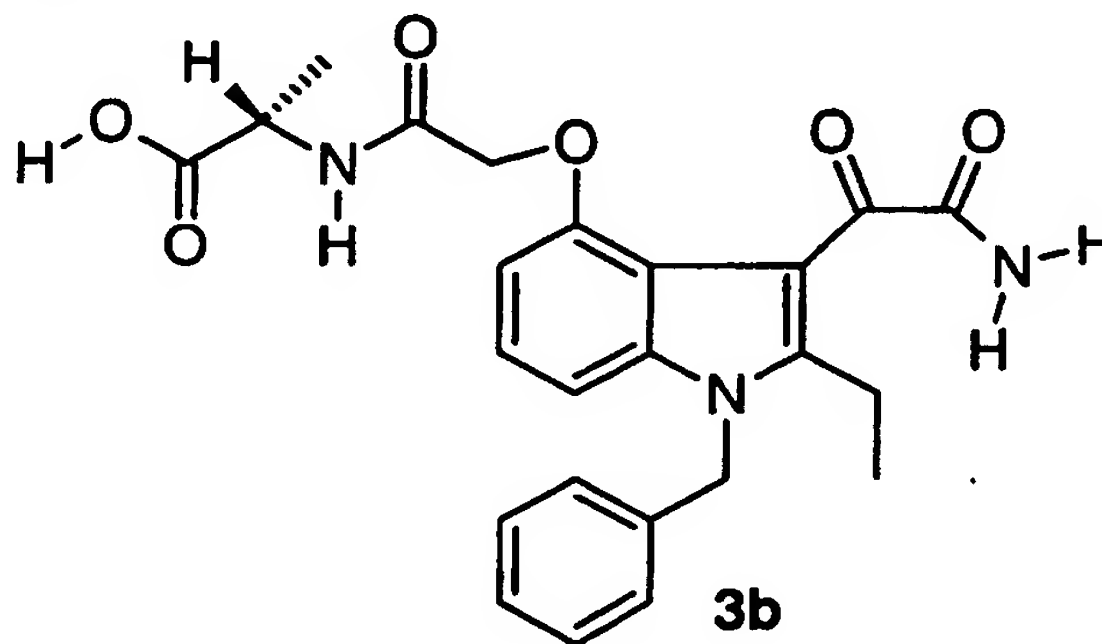
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2H), 6.57 (m, 1H), 6.99 (d, $J = 7.4$ Hz, 2H), 7.07-7.08 (m, 2H), 7.21-7.31 (m, 3H), 7.56 (s, 1H), 8.05 (s, 1H), 8.40 (d, $J = 6.8$ Hz, 1H).

5 **B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine**

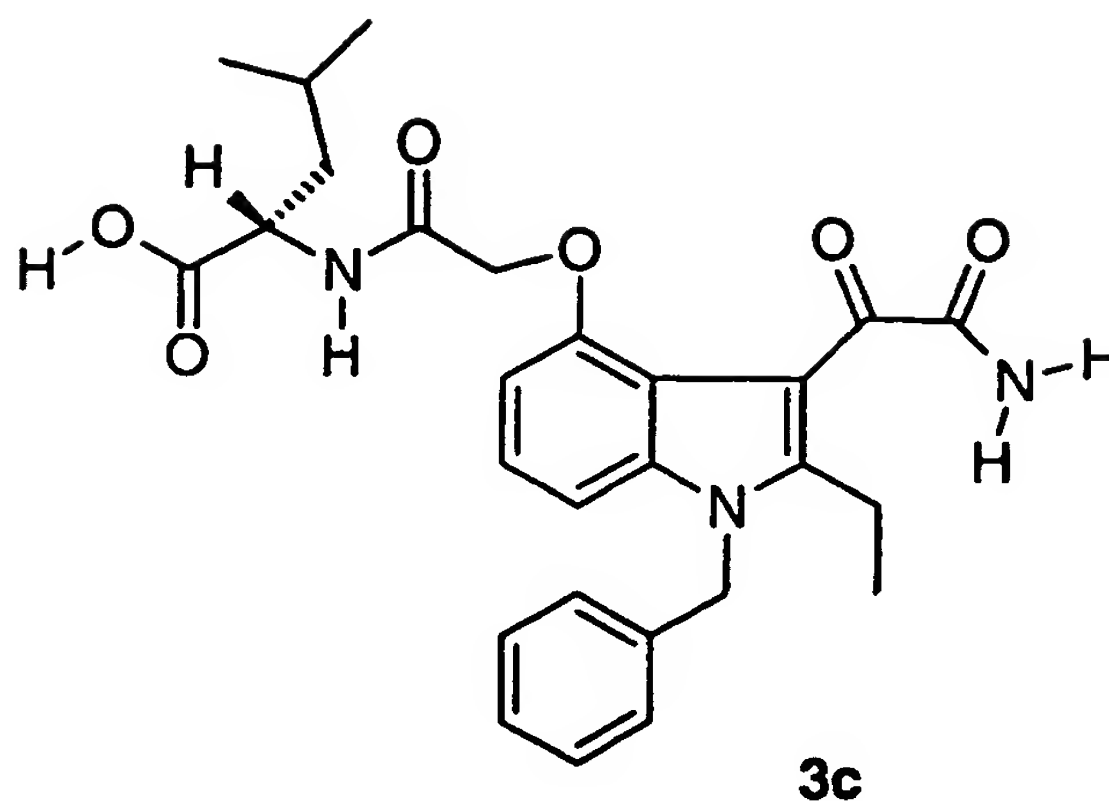


Following the experimental procedure as described for
10 preparing compound 3a, compound 3b, was obtained as a
yellow solid in 89% yield. ^1H NMR (DMSO- d_6) δ 1.04 (t, J
= 7.2 Hz, 3H), 1.29 (d, $J = 7.3$ Hz, 3H), 2.91 (br q, $J =$
7.2 Hz, 2H), 4.22 (td, $J = 7.2, 7.1$ Hz, 1H), 4.54 (s, 2H),
5.51 (s, 2H), 6.60 (d, $J = 6.3$ Hz, 1H), 7.00-7.09 (m, 4H),
15 7.21-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.31 (d, J
= 7.1 Hz, 1H), 12.75-12.84 (br s, 1H).

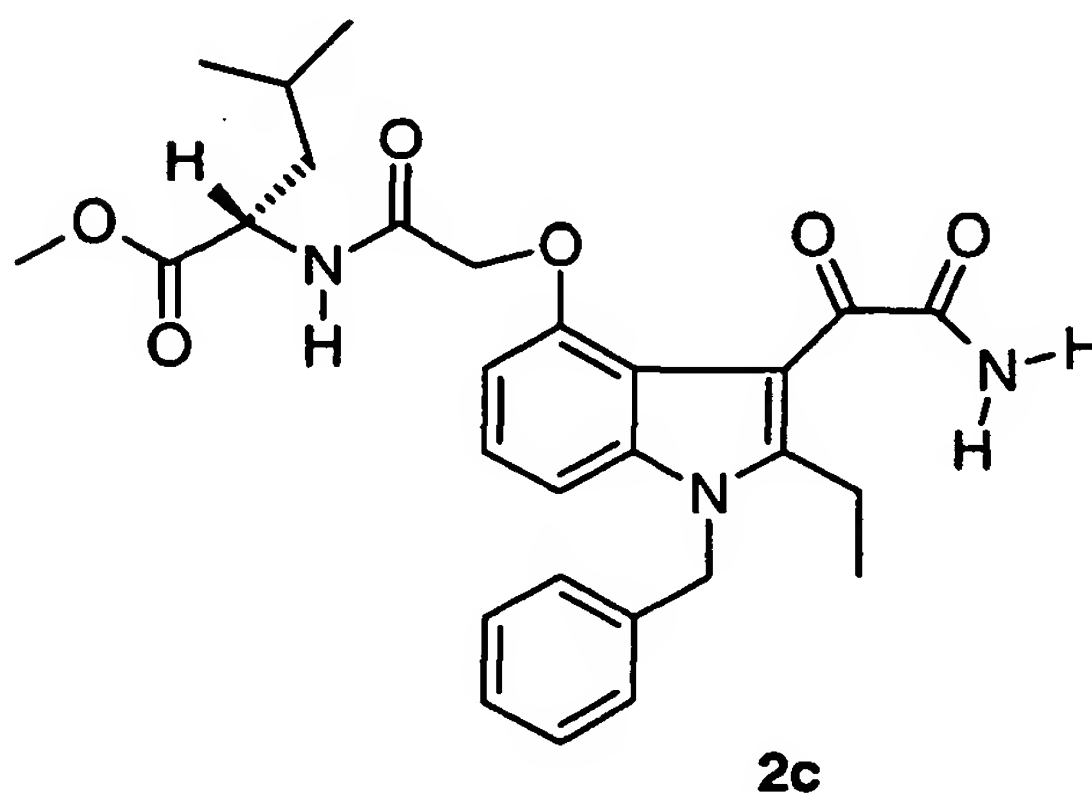
Example 5

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
20 indol-4-yl]oxy]acetyl]-L-leucine

-94-



A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester



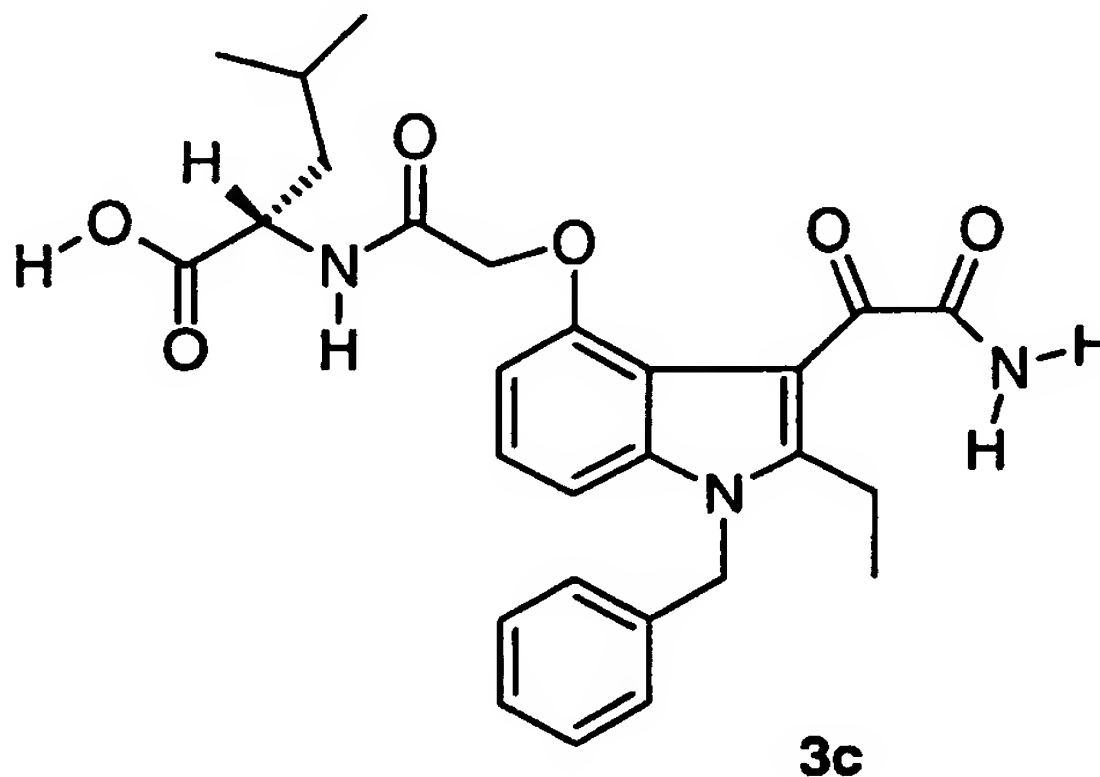
5

Following the experimental procedure as described for 2a, 2c was obtained as a yellow solid in 98% yield. ¹H NMR (DMSO-d₆) δ 0.67 (d, *J* = 5.5 Hz, 3H), 0.72 (d, *J* = 5.7 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.51-1.64 (m, 1H), 2.91 (br q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 4.20-4.27 (m, 1H), 4.57 (s, 2H), 5.52 (s, 2H), 6.53-6.56 (m, 1H), 6.97-7.08 (m, 4H), 7.21-7.29 (m, 3H), 7.56 (s, 1H), 8.07 (s, 1H), 8.37 (d, *J* = 7.3 Hz, 1H).

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B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine



5 Following the experimental procedure as described for 3a, 3c was obtained as a yellow solid in 75% yield. ¹H NMR (DMSO-d₆) δ 0.76 (d, J = 5.7 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.39-1.43 (m, 1H), 1.69 (t, J = 7.3 Hz, 2H), 2.96 (br q, J = 7.3 Hz, 2H), 4.57-4.65 (m, 1H), 4.69 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 5.38 (s, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.95-7.12 (m, 5H), 7.26-7.32 (m, 3H), 8.17 (d, J = 8.2 Hz, 1H).

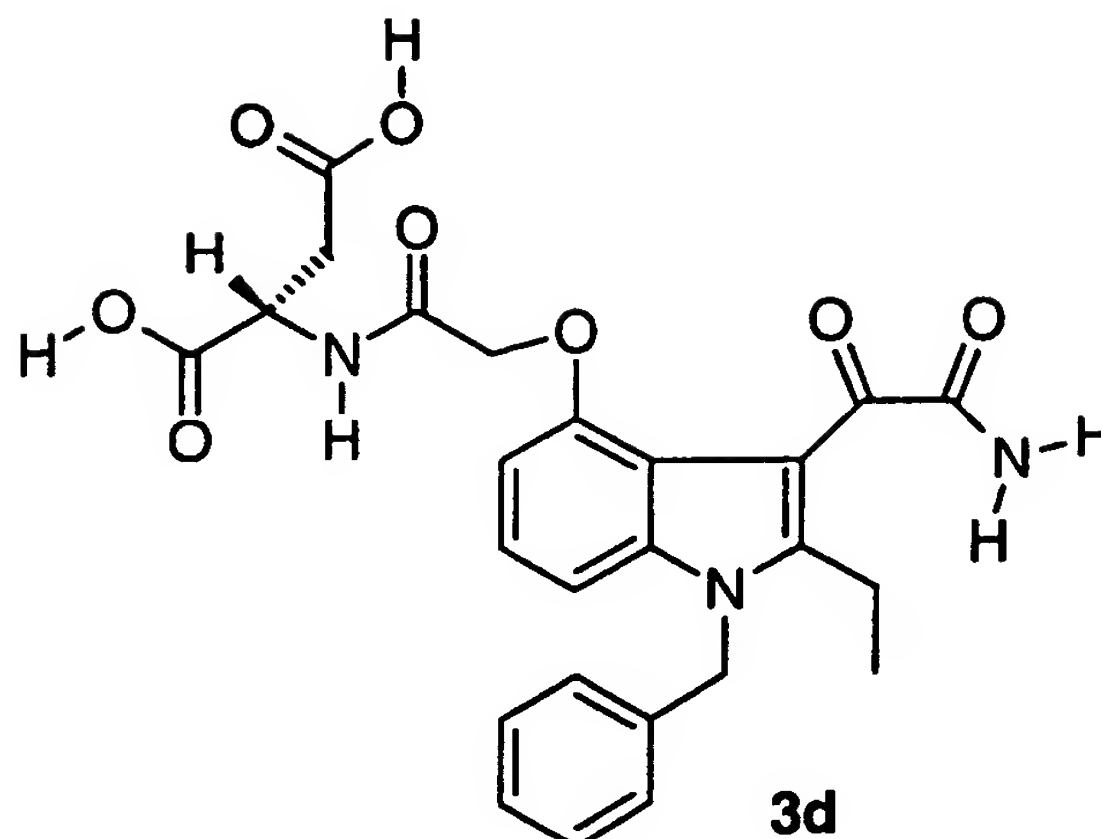
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Example 6

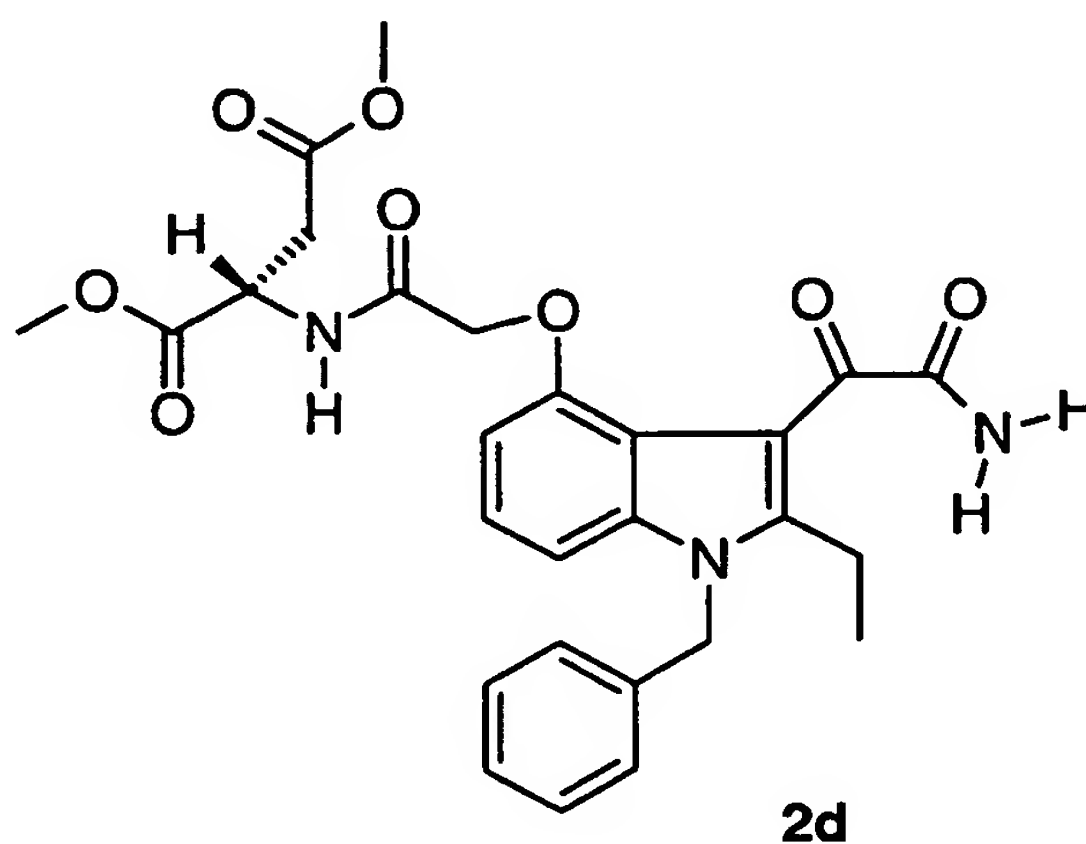
N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid

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A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester



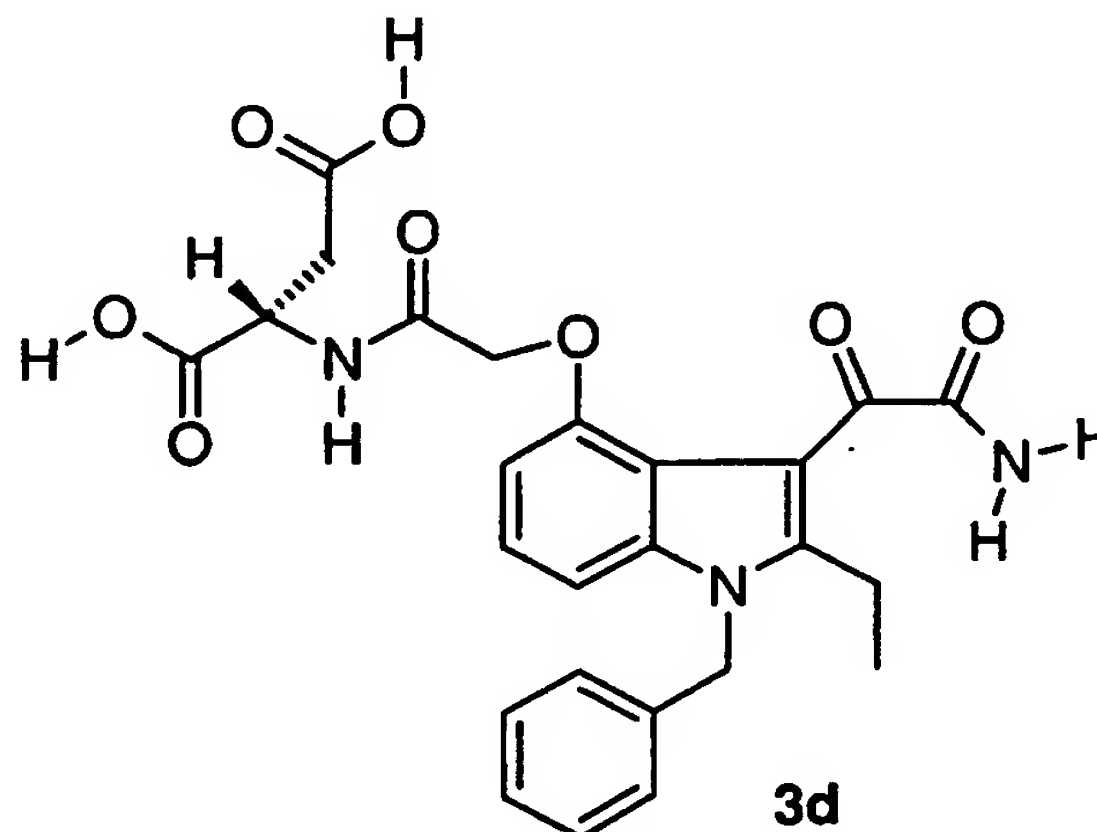
5

Following the experimental procedure as described for 2a, 2d was obtained as a yellow solid in 88% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.3 Hz, 3H), 2.72 (dd, J = 16.6, 7.1 Hz, 1H), 2.83 (dd, J = 16.7, 7.1 Hz, 1H), 2.90 (br q, J = 7.3 Hz, 2H), 3.49 (s, 3H), 3.55 (s, 3H), 4.54 (s, 2H), 4.66 (m, 1H), 5.51 (s, 2H), 6.54 (m, 1H), 6.97-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.50 (s, 1H), 7.97 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H).

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B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid



5

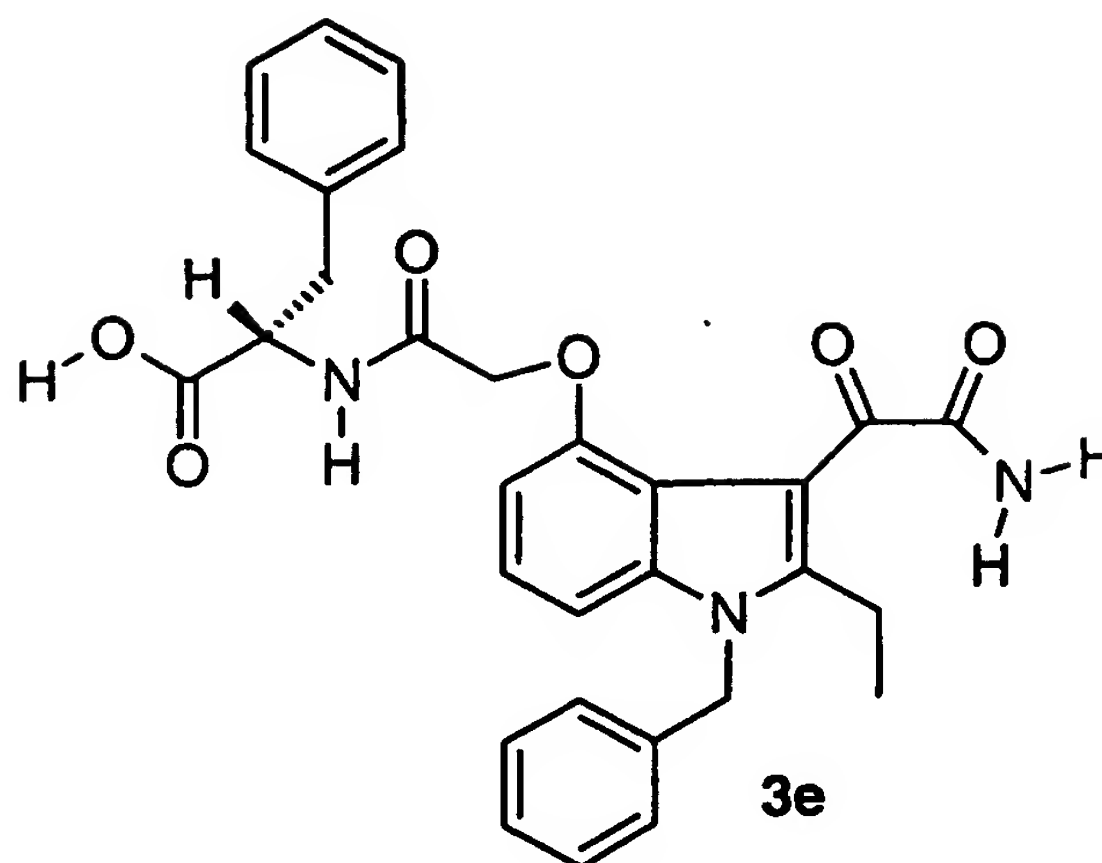
Following the experimental procedure as described for 3a, 3d was obtained as a yellow solid in 99% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, *J* = 7.2 Hz, 3H), 2.52-2.76 (m, 2H), 2.90 (br q, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 4.53-4.60 (m, 1H), 5.50 (s, 2H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.19-7.30 (m, 3H), 7.47 (s, 1H), 7.94 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 12.40-13.20 (br s, 2H).

Example 7

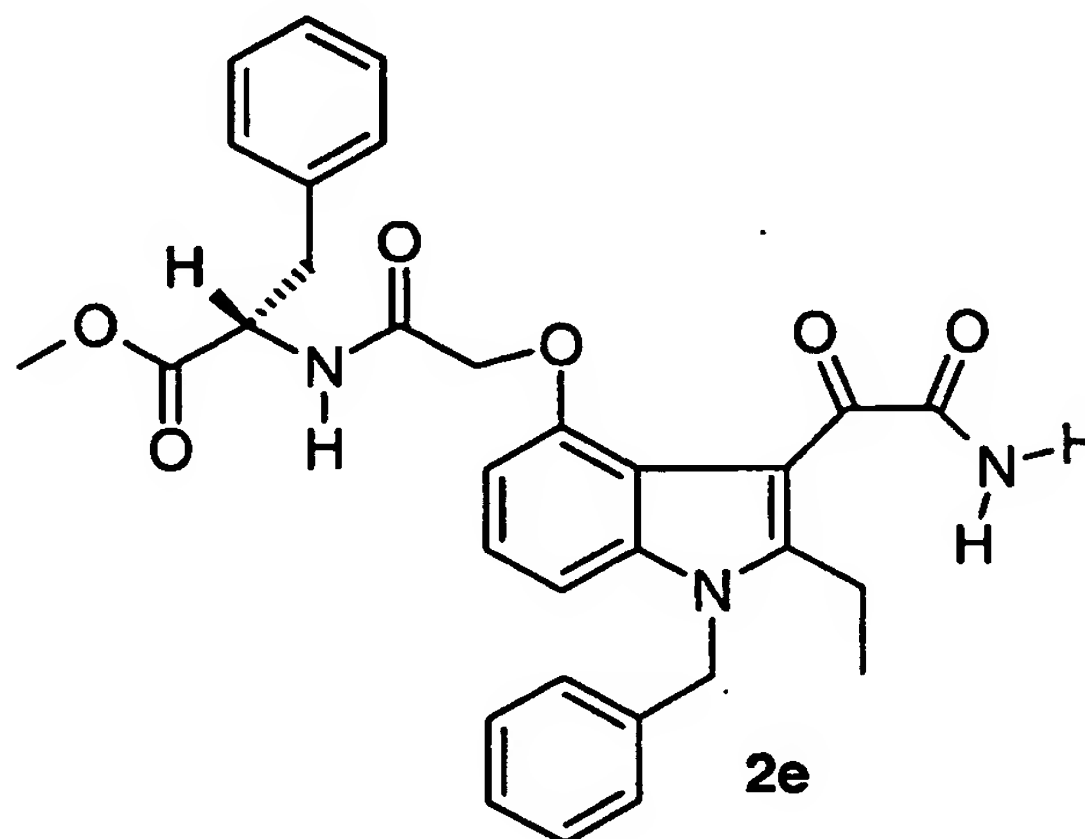
***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine**

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A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester



5

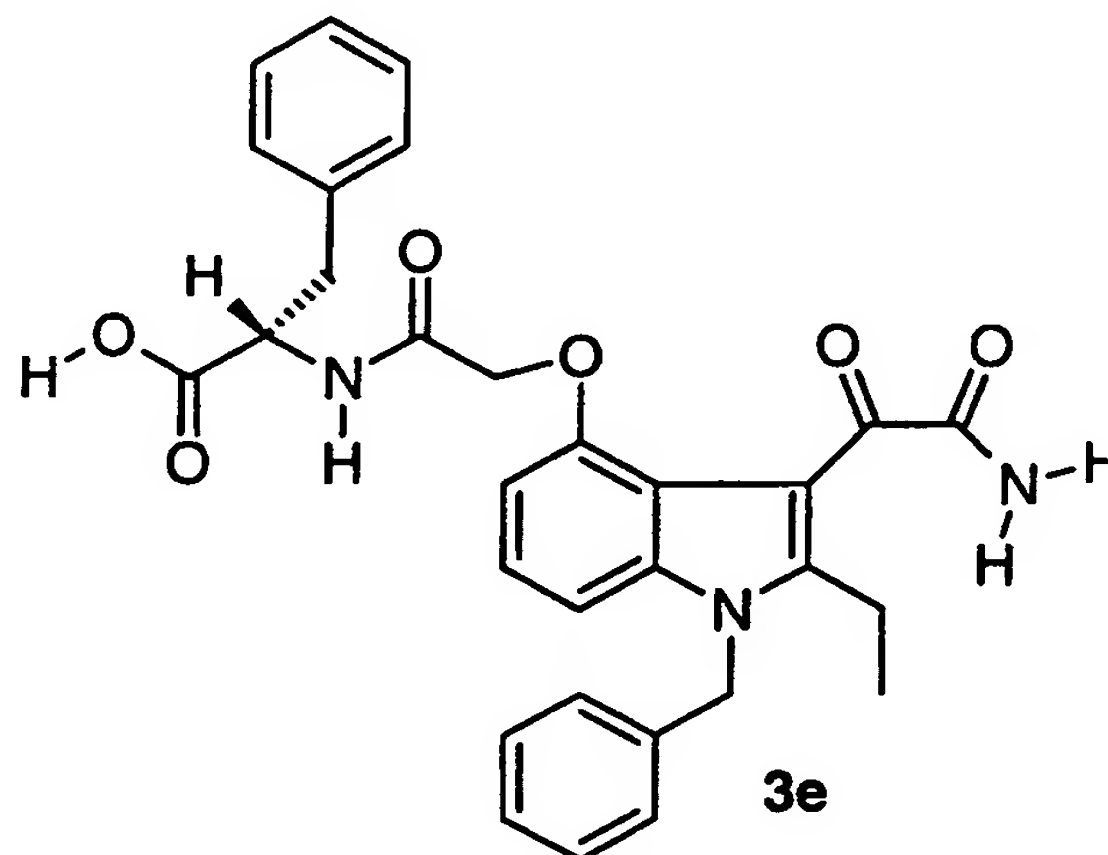
Following the experimental procedure as described for 2a, 2e was obtained as a yellow solid in 68% yield. ¹H NMR (DMSO-d₆) δ 1.06 (t, J = 7.2 Hz, 3H), 2.88-3.03 (m, 4H), 3.54 (s, 3H), 4.47-4.50 (m, 1H), 4.50 (s, 2H), 5.52 (s, 2H), 6.41 (d, J = 7.7 Hz, 1H), 6.98-7.11 (m, 9H), 7.21-7.30 (m, 3H), 7.47 (s, 1H), 8.06 (s, 1H), 8.52 (d, J = 7.7 Hz, 1H).

10

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B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine



5

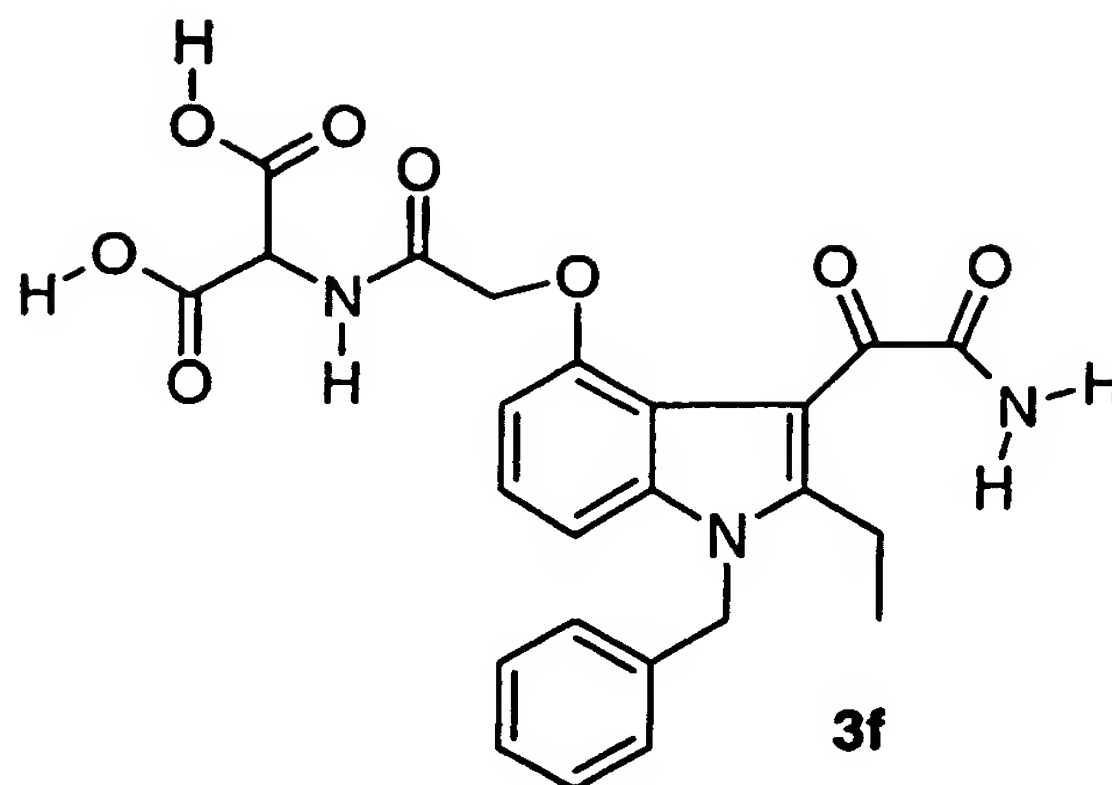
Following the experimental procedure as described for 3a, 3e was obtained as a yellow solid in 93% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.1 Hz, 3H), 2.85-3.12 (m, 4H), 4.17-4.26 (m, 1H), 4.54 (s, 2H), 5.51 (s, 2H), 6.59 (d, J = 6.4 Hz, 1H), 6.98-7.09 (m, 9H), 7.19-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.30 (d, J = 7.0 Hz, 1H), 12.50 (br s, 1H).

Example 8

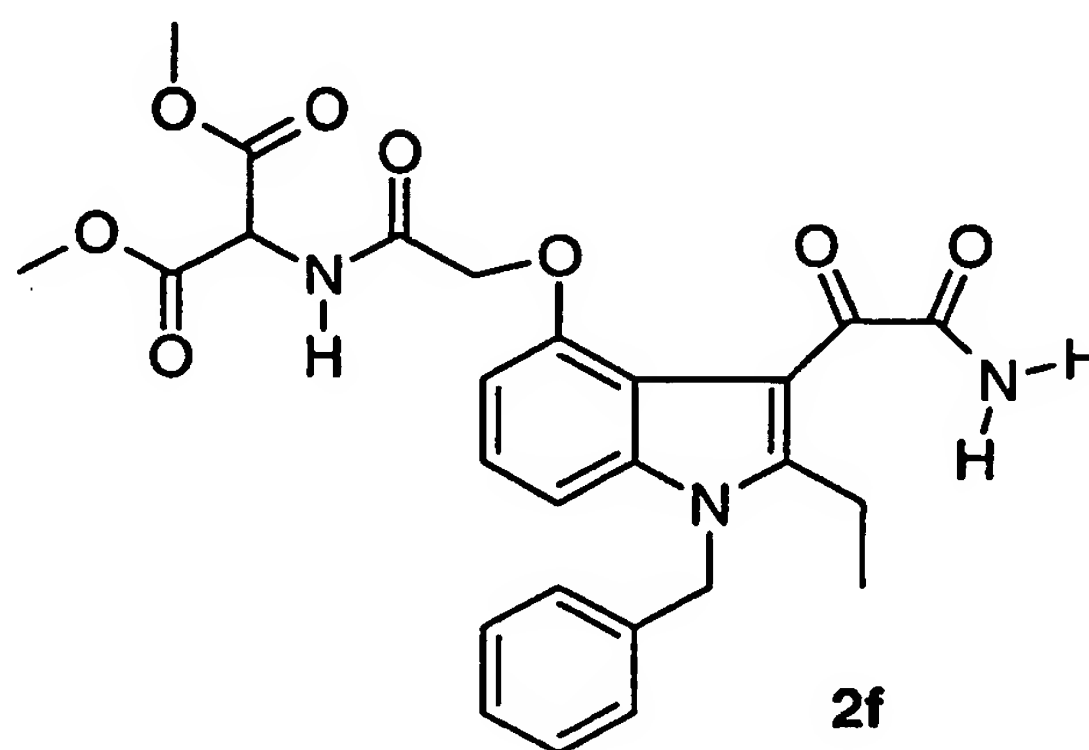
15 **[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid**

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A. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester



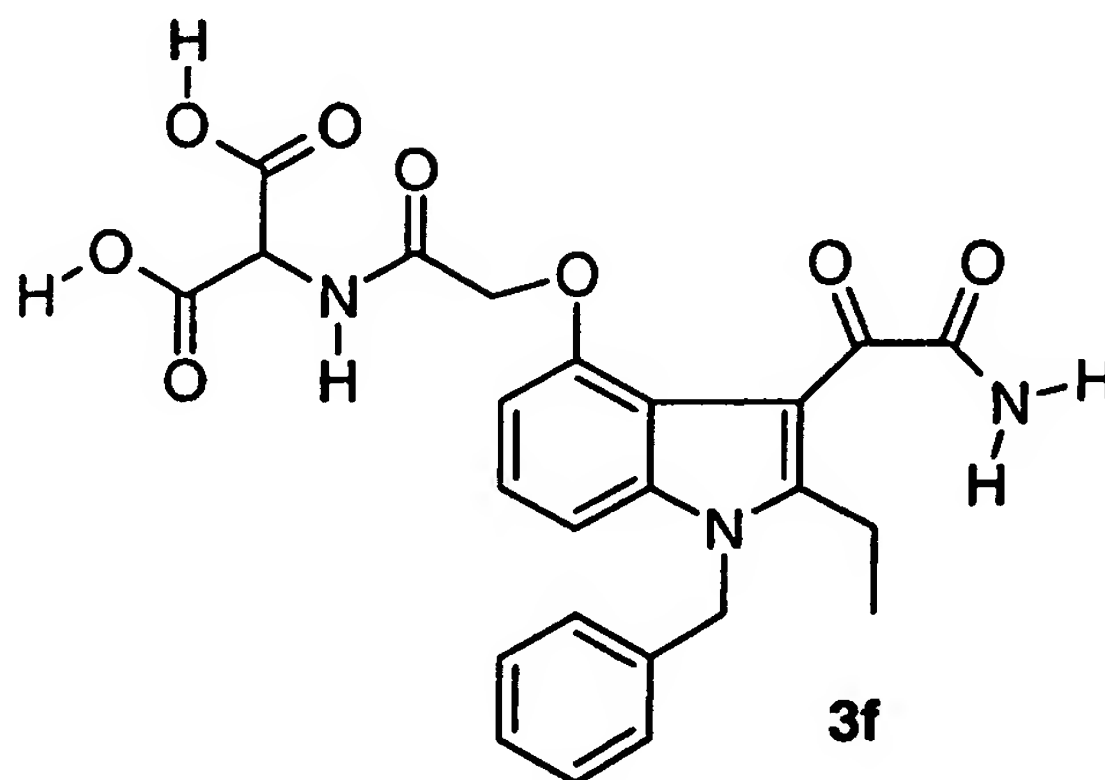
5

Following the experimental procedure as described for 2a, 2f was obtained as a yellow solid in 98% yield. ^1H NMR (DMSO- d_6) δ 1.04 (t, J = 7.3 Hz, 3H), 2.90 (br q, J = 7.3 Hz, 2H), 3.64 (s, 6H), 4.63 (s, 2H), 5.16 (d, J = 7.1 Hz, 1H), 5.51 (s, 2H), 6.54-6.56 (m, 1H), 6.98-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.43 (s, 1H), 7.88 (s, 1H), 8.90 (d, J = 7.2 Hz, 1H).

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B. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid



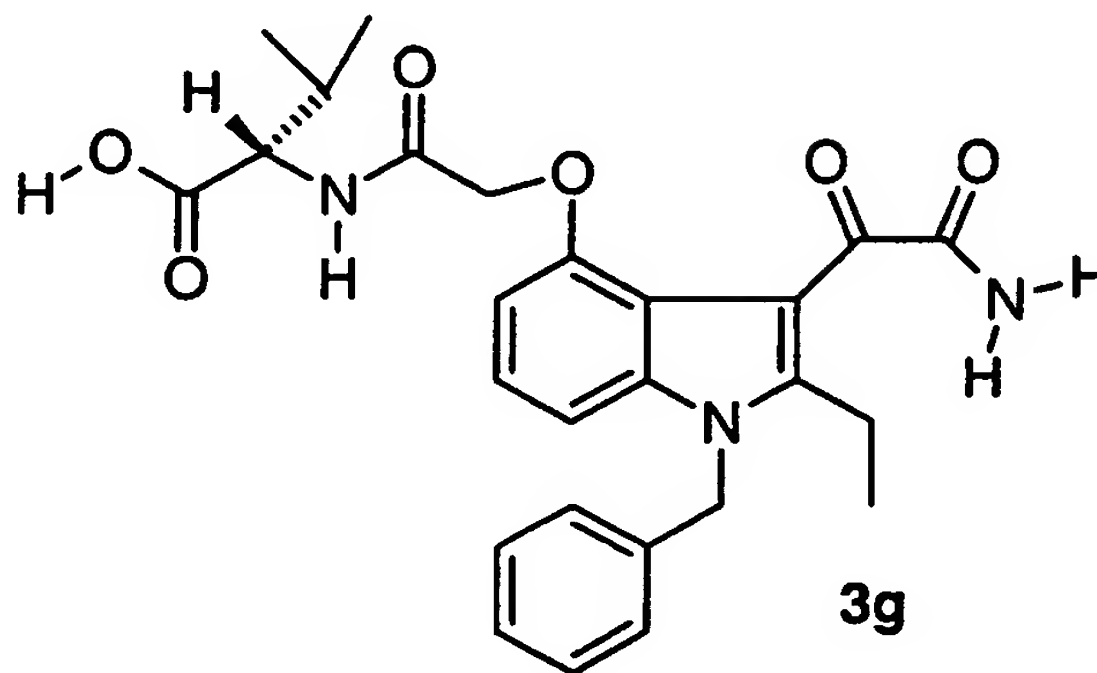
Following the experimental procedure as described for 3a,
5 3f was obtained as a yellow solid in 99% yield. ¹H NMR
(DMSO-d₆) δ 1.04 (t, J = 6.9 Hz, 3H), 2.89 (br q, J = 7.3
Hz, 2H), 4.62 (s, 2H), 4.91 (d, J = 7.2 Hz, 1H), 5.50 (s, .
2H), 6.57 (d, J = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.18-
7.30 (m, 3H), 7.37 (s, 1H), 7.83 (s, 1H), 8.55 (d, J = 7.2
10 Hz, 1H), 12.30-13.00 (br s, 2H).

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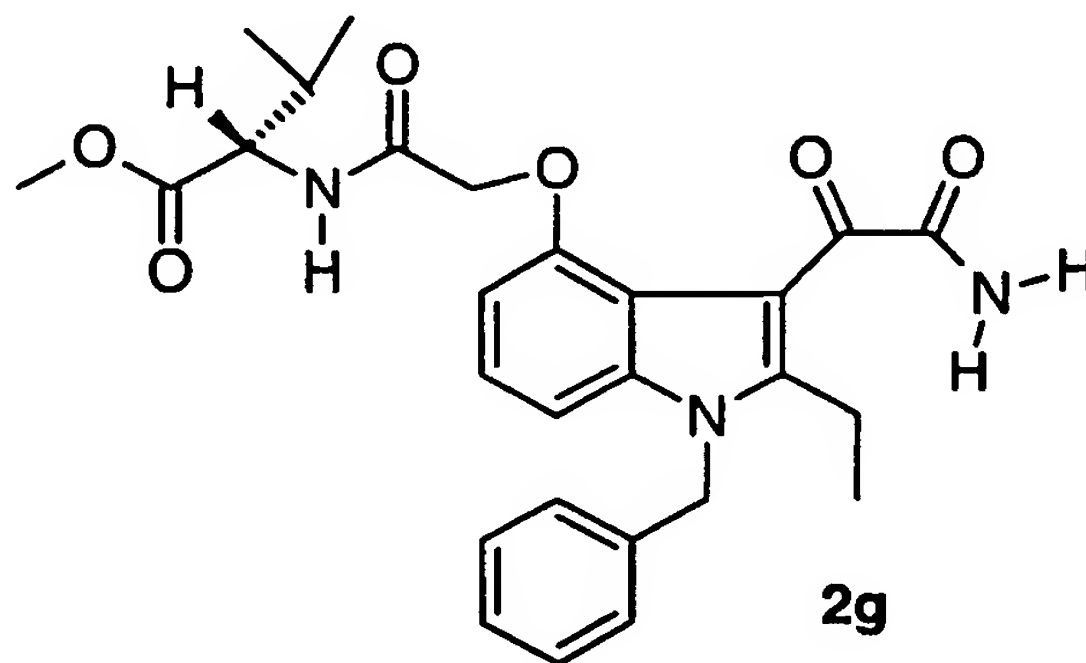
Example 9

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine**



5

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester



10 Following the experimental procedure as described for 2a, 2g was obtained as a yellow solid in 96% yield. ¹H NMR (DMSO-d₆) δ 0.71 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.2 Hz 3H), 1.99-2.05 (m, 1H), 2.90 (br q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 4.11 (br t, *J* = 7.0 Hz, 1H), 4.60 (s, 2H), 5.52 (s, 2H), 6.52 (d, *J* = 4.4 Hz, 1H),

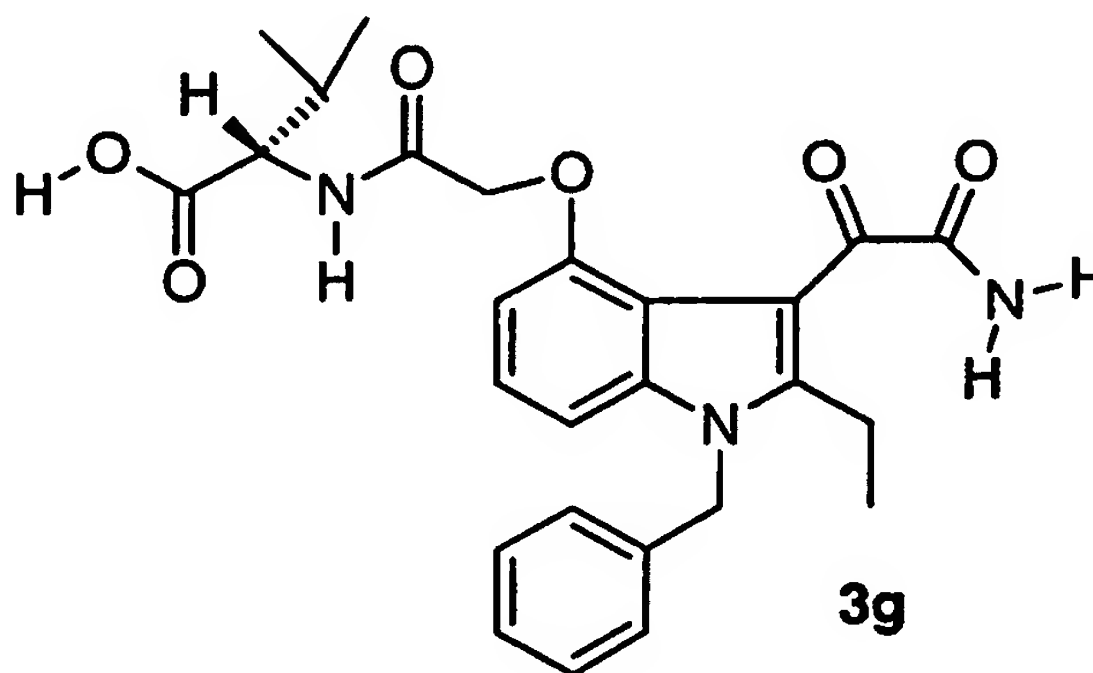
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6.95 (d, $J = 7.2$ Hz, 2H), 7.06 (br s, 2H), 7.18-7.29 (m, 3H), 7.52 (s, 1H), 8.04 (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminoxyacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine



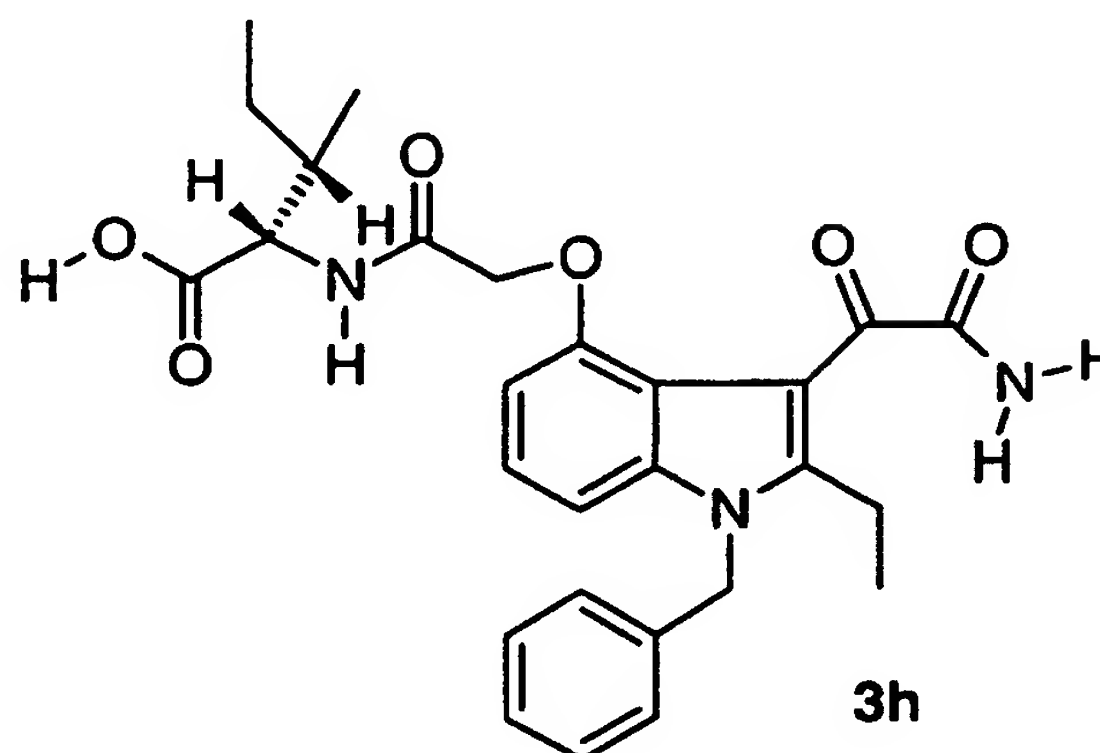
Following the experimental procedure as described for 3a, 3g was obtained as a yellow solid in 94% yield. ^1H NMR (DMSO- d_6) δ 0.71 (d, $J = 6.9$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H), 2.01-2.07 (m, 1H), 2.90 (br q, $J = 7.3$ Hz, 2H), 4.09 (br dd, $J = 7.9, 6.2$ Hz, 1H), 4.60 (s, 2H), 5.51 (s, 2H), 6.54 (d, $J = 6.1$ Hz, 1H), 6.95 (d, $J = 7.3$ Hz, 2H), 6.99-7.08 (m, 2H), 7.18-7.29 (m, 3H), 7.49 (s, 1H), 8.01 (s, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 12.63 (br s, 1H).

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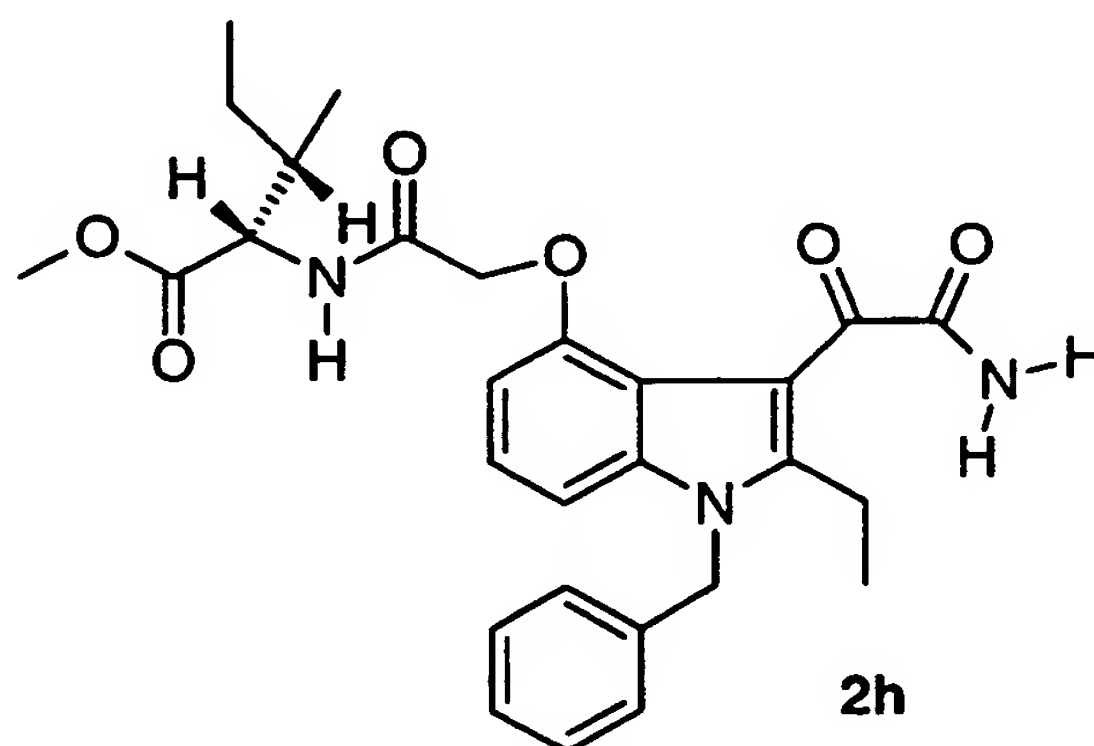
Example 10

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine**



5

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester



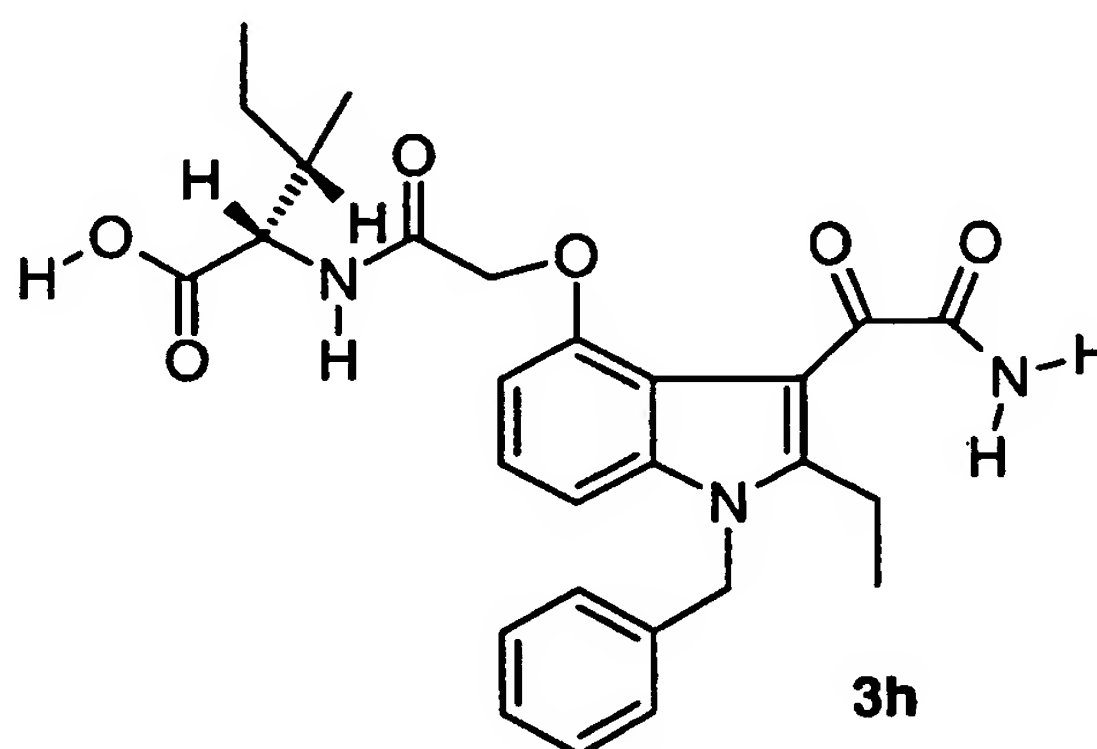
- 10 Following the experimental procedure as described for 2a, 2h was obtained as a yellow solid in 73% yield. ¹H NMR (DMSO-d₆) δ 0.64-0.71 (m, 6H), 0.99-1.08 (m, 4H), 1.21-1.26 (m, 1H), 1.76-1.80 (m, 1H), 2.91 (br q, *J* = 7.4 Hz, 2H), 3.53 (s, 3H), 4.15 (br t, *J* = 7.2 Hz, 1H), 4.60 (s,

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2H), 5.52 (s, 2H), 6.52 (m, 1H), 6.96 (d, $J = 7.2$ Hz, 2H), 7.02-7.07 (m, 2H), 7.18-7.29 (m, 3H), 7.53 (s, 1H), 8.04 (s, 1H), 8.23 (d, $J = 7.7$ Hz, 1H).

5 **B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine**



Following the experimental procedure as described for 3a,
10 3h was obtained as a yellow solid in 92% yield. ^1H NMR
(DMSO- d_6) δ 0.64-0.84 (m, 6H), 1.04 (t, $J = 7.2$ Hz, 3H),
1.21-1.28 (m, 2H), 1.76-1.80 (m, 1H), 2.91 (br q, $J = 7.2$
Hz, 2H), 4.12 (br t, $J = 7.3$ Hz, 1H), 4.59 (s, 2H), 5.51
(s, 2H), 6.55 (d, $J = 6.4$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz,
15 2H), 7.01-7.08 (m, 2H), 7.21-7.29 (m, 3H), 7.51 (s, 1H),
8.01 (s, 1H), 8.11 (d, $J = 7.4$ Hz, 1H), 12.40-12.65 (br s,
1H).

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Assay

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A₂. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A₂ on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

15 Reagents:

REACTION BUFFER -

CaCl₂·2H₂O (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)

20 (Sigma A-7030, product of Sigma
Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

25 0.05 NaOAc·3H₂O, pH 4.5

0.2 NaCl

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Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

5 racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-glycero-3-phosphorylcholine

TRITON X-100™ prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

10 A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

TRITON X-100™ nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB
15 to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mM Triton X-100™ detergent, and 0.12 mM DTMB in a buffered aqueous solution at pH 7.5.

20

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
- 25 3. Add 50 nanograms of sPLA₂ (10 microliters) to appropriate wells;

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4. Incubate plate at 40 °C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

5 All compounds were tested in triplicate.

Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC₅₀ values were determined. Typically, the IC₅₀ values (see, Table I, below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC₅₀ values. IC₅₀ were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition.

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Results of Human Secreted Phospholipase A₂ Inhibition
Tests

Table

Compound No. from Examples 3-10	Inhibition of human secreted PLA ₂ IC ₅₀ ± mean deviation (3-4 tests) (nM)
1	49
2A	529
2B	533
2C	82
2D	874
2E	666
2F	698
2G	283
2H	166
3A	71
3B	59
3C	28
3D	132
3E	64
3F	44.7
3G	36.4
3H	25.1

5 The compound of Example 1 is highly active in
inhibiting sPLA₂.

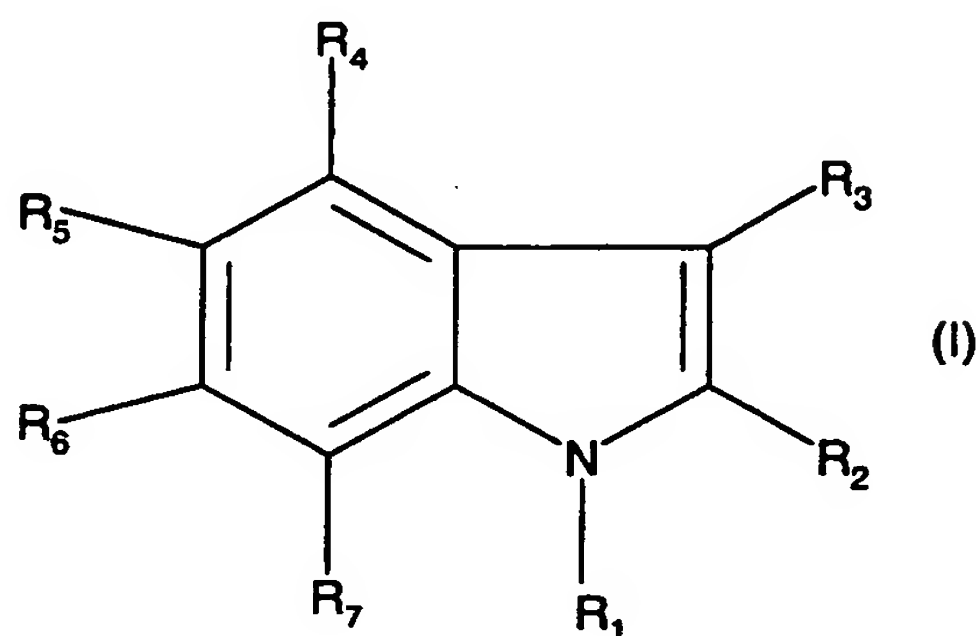
While the present invention has been illustrated
above by certain specific embodiments, it is not intended
10 that these specific examples should limit the scope of the
invention as described in the appended claims.

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WE CLAIM:

1. An indole compound represented by the formula
(I), or a pharmaceutically acceptable salt, solvate, or
5 prodrug derivative thereof;



wherein ;

- 10 R₁ is selected from groups (a), (b), and (c)

wherein;

(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

- 15 (b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

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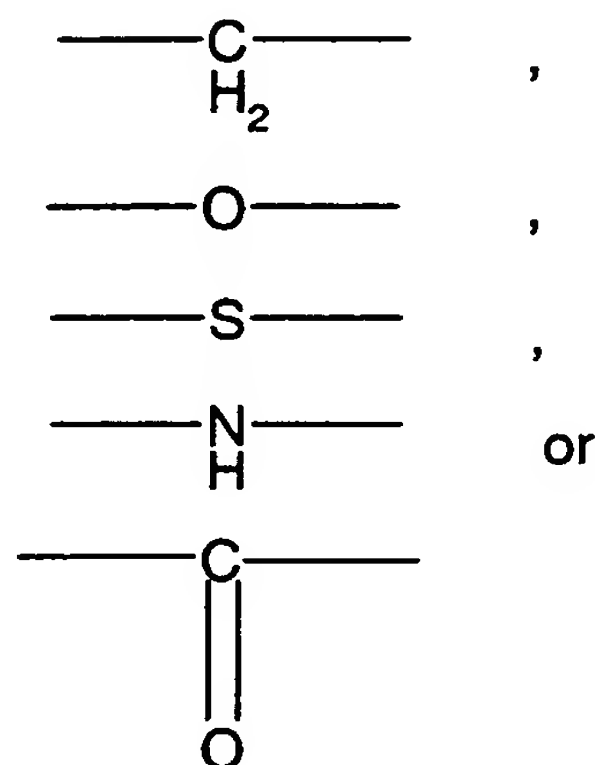
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(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

5 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

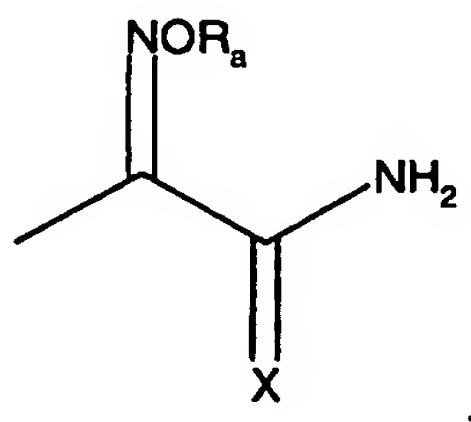
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:

10



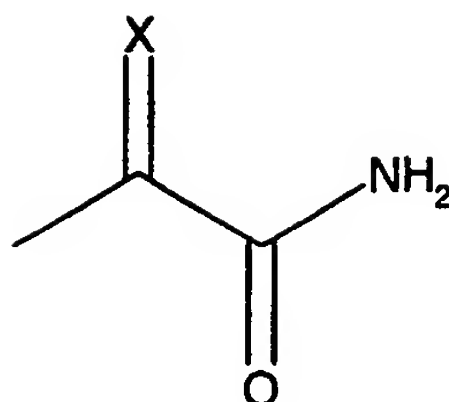
and Z is selected from a group represented by the formulae,

15



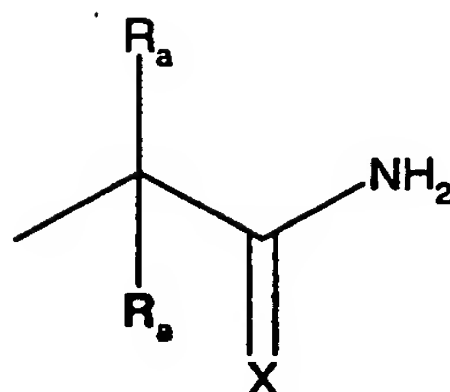
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or

5



wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R_4 is the group, $-(L_C)-(acylamino\ acid\ group)$; wherein $-(L_C)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein
15 $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),

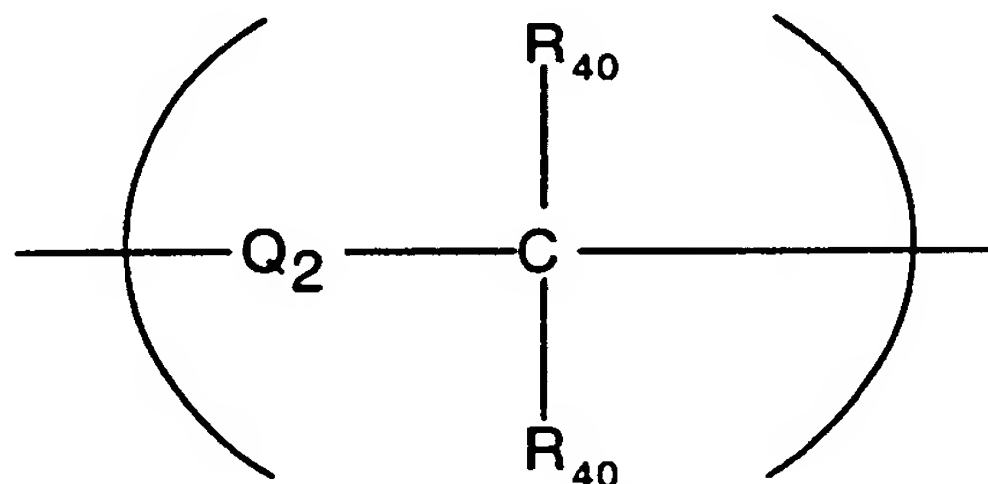
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heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

2. The compound of claim 1 wherein R_2 is
5 hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, $-O-(C_1-C_3 \text{ alkyl})$,
 $-S-(C_1-C_3 \text{ alkyl})$, C_3 - C_4 cycloalkyl, $-CF_3$, halo, $-NO_2$, $-CN$, or $-SO_3$.

3. The compound of Claim 1 wherein the acylamino
10 acid linker group, $-(L_C)-$, for R_4 is selected from a
group represented by the formula;

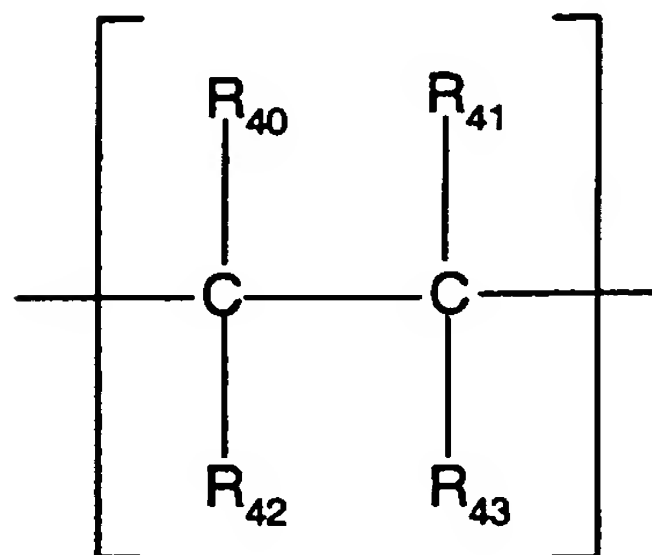
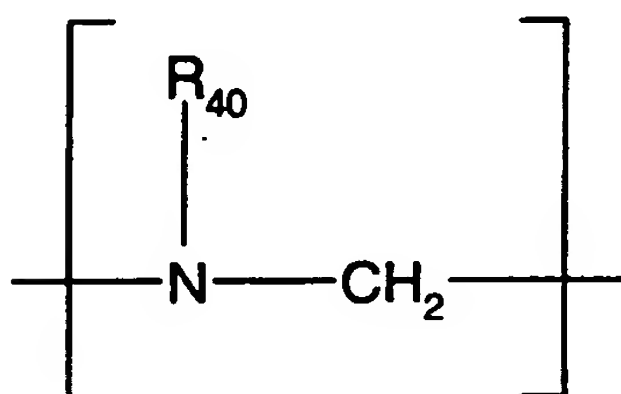
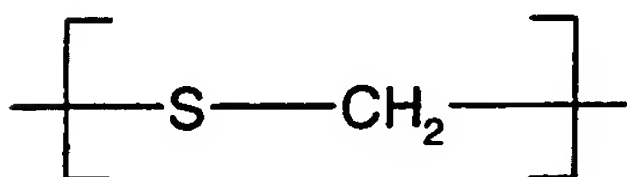
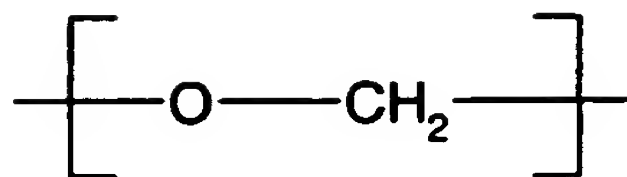


15 where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$,
 $-C(O)-$, and $-S-$, and each R_{40} is independently selected
from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8
alkoxy, aralkyl, and halo.

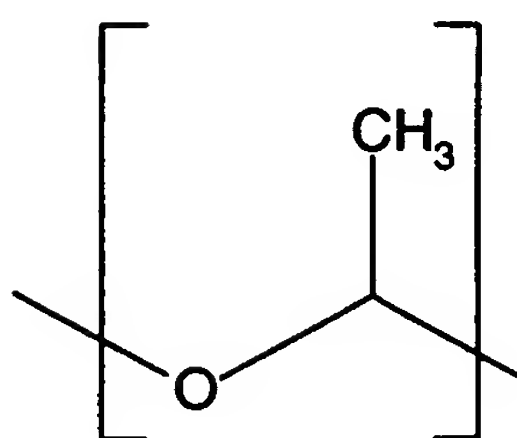
20 4. The compound of Claim 1 wherein the acylamino
acid linker group, $-(L_C)-$, for R_4 selected from $-(L_C)-$
is a divalent group selected from,

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or



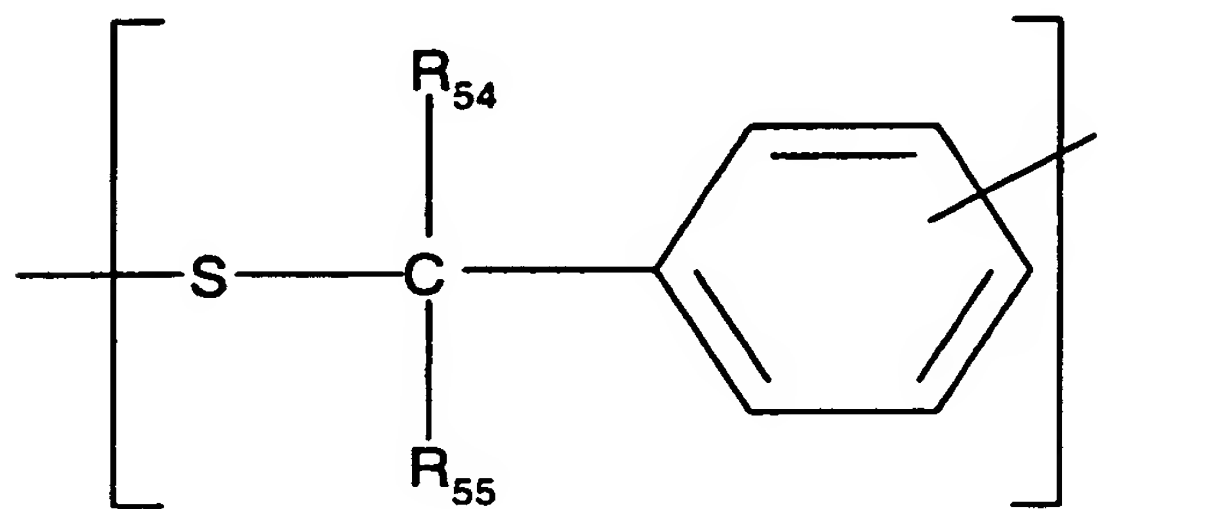
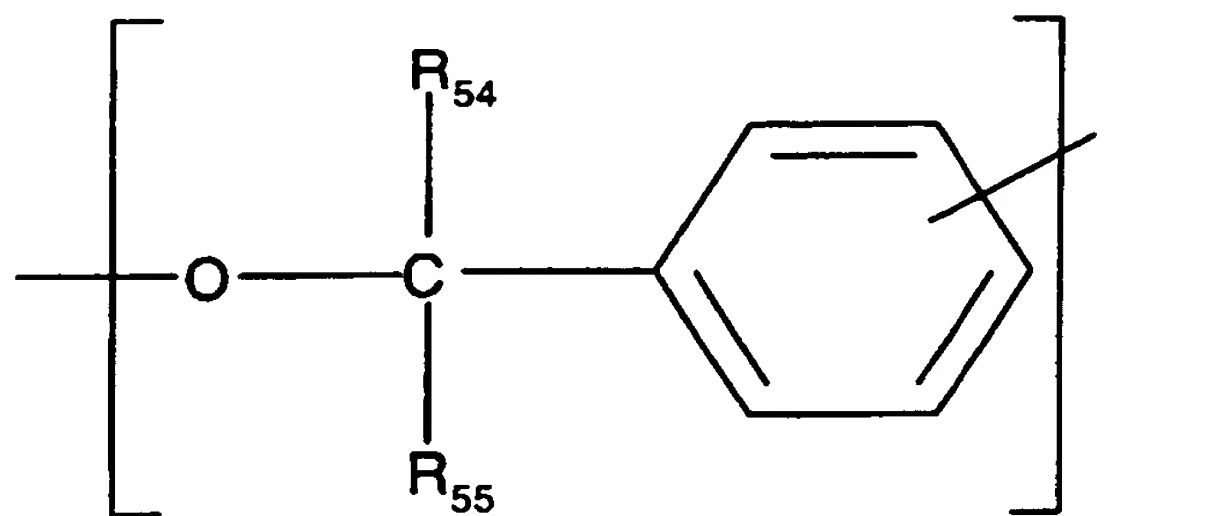
5

where R_{40} , R_{41} , R_{42} , and R_{43} are each independently selected from hydrogen, C_1 - C_8 alkyl.

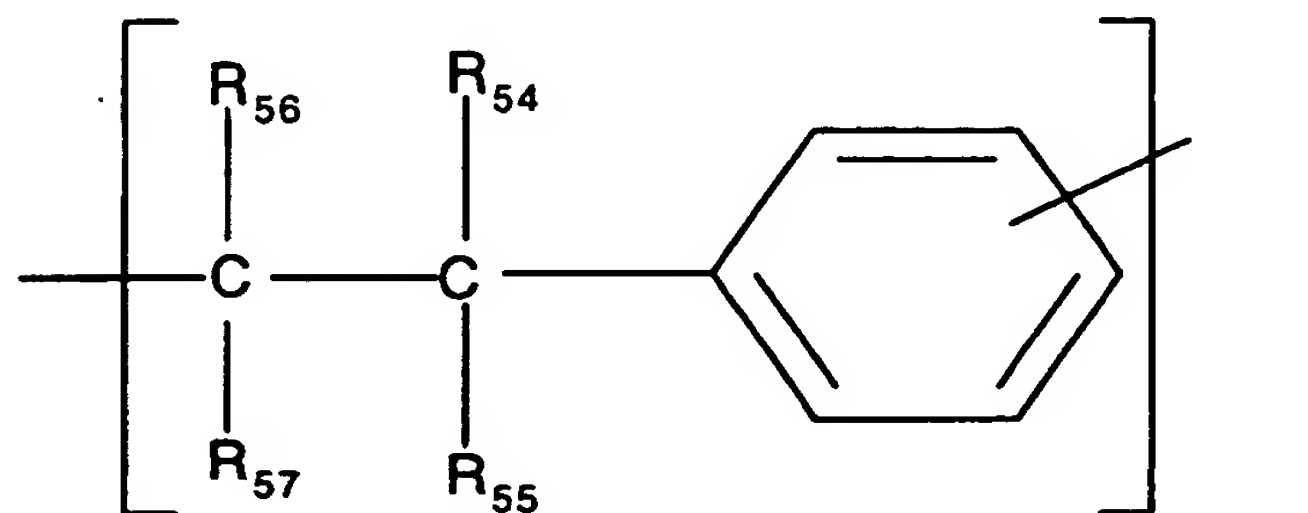
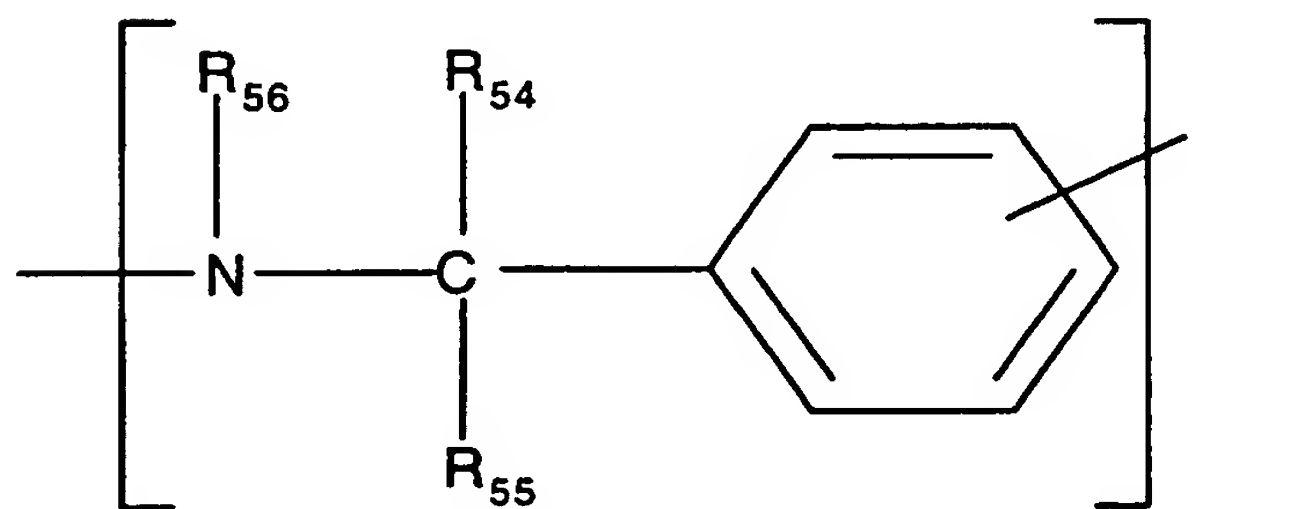
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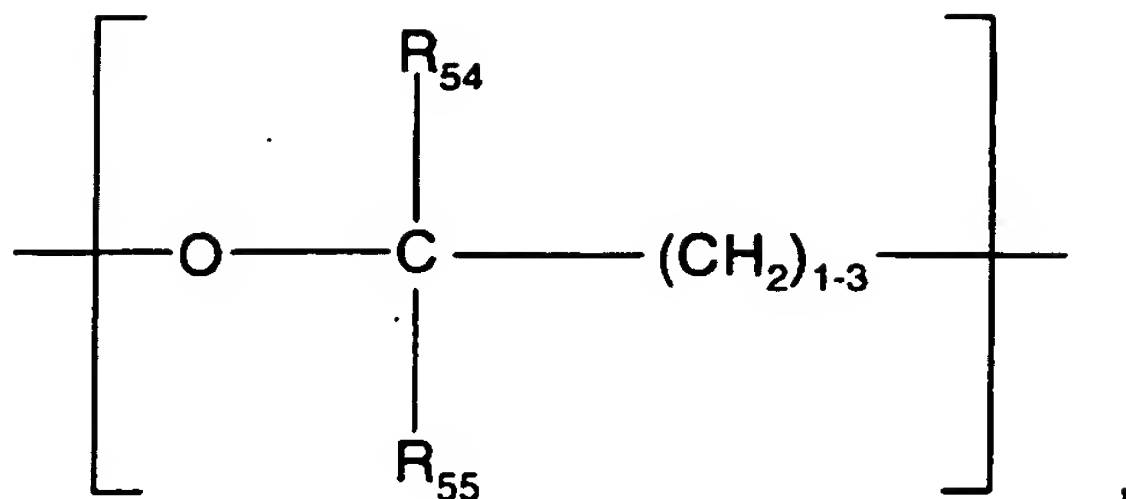
5. The compound of Claim 1 wherein the acid linker, $-(L_a)-$, for R_5 is selected from a group represented by the formulae consisting of;



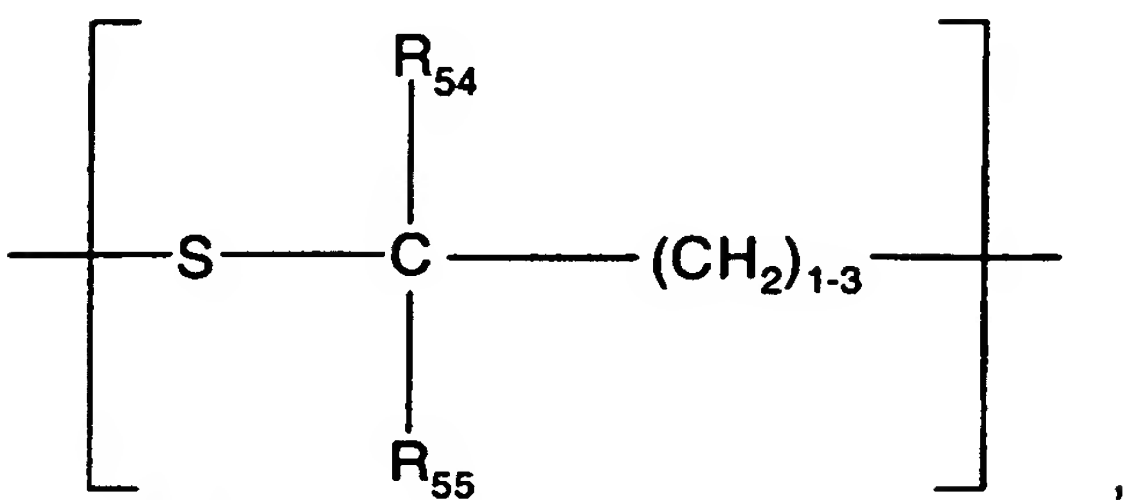
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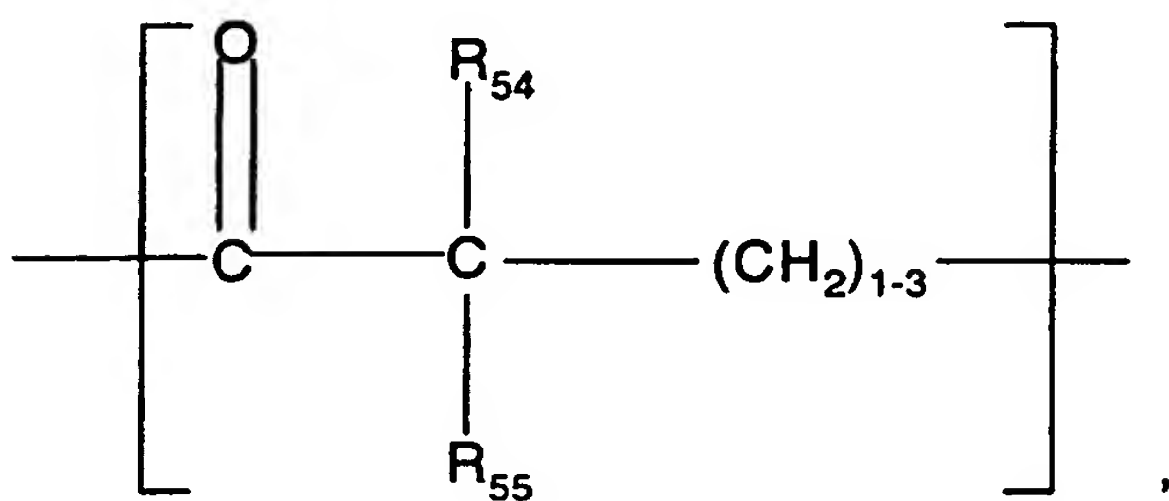
-116-



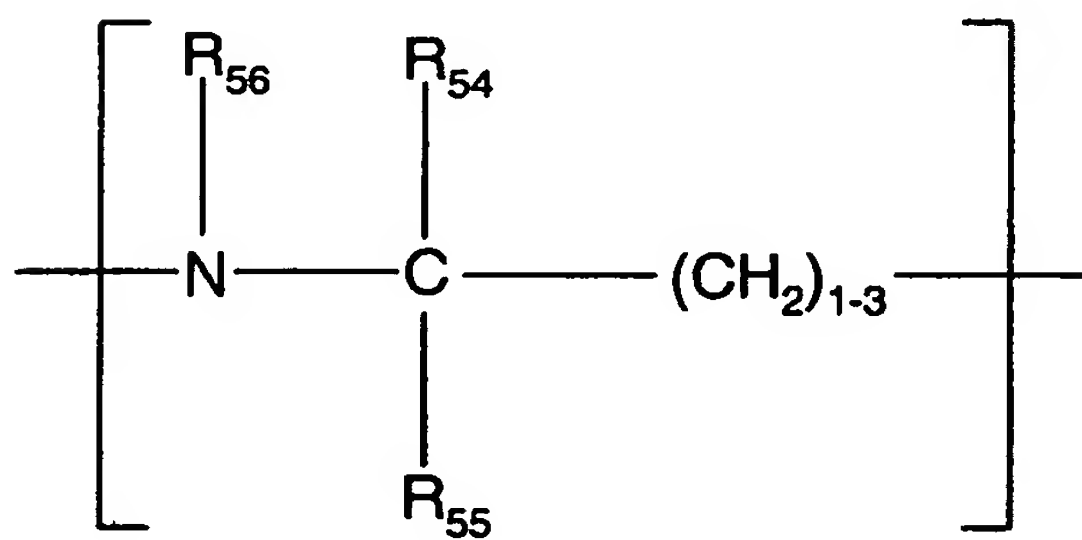
,



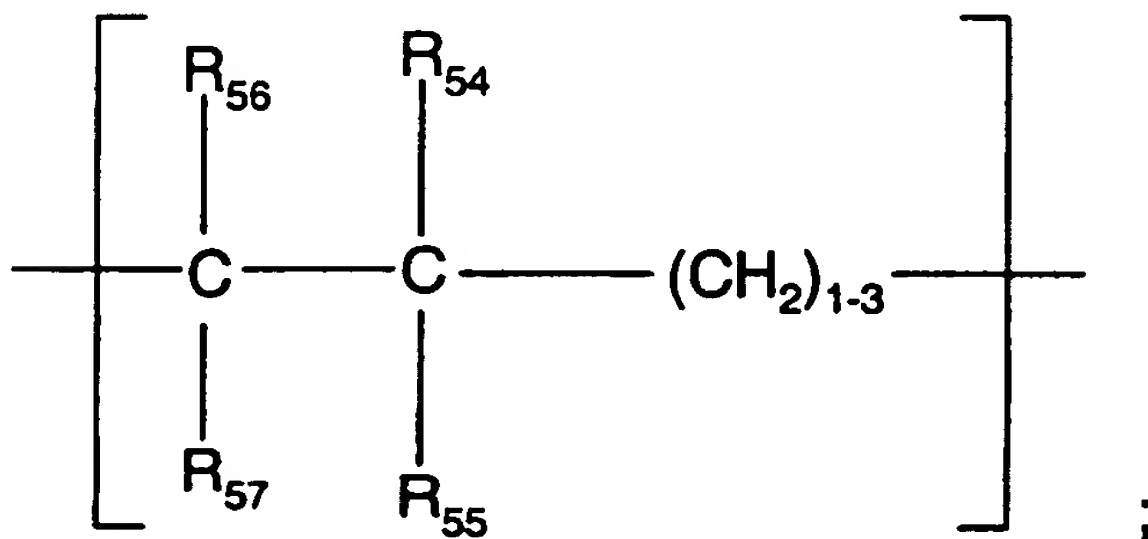
,



,



and



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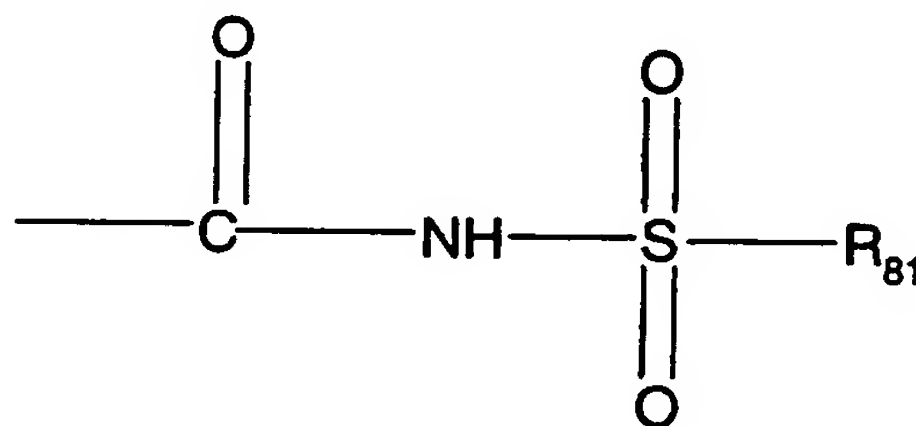
wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo.

- 5 6. The compound of claim 1 wherein R₅ is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

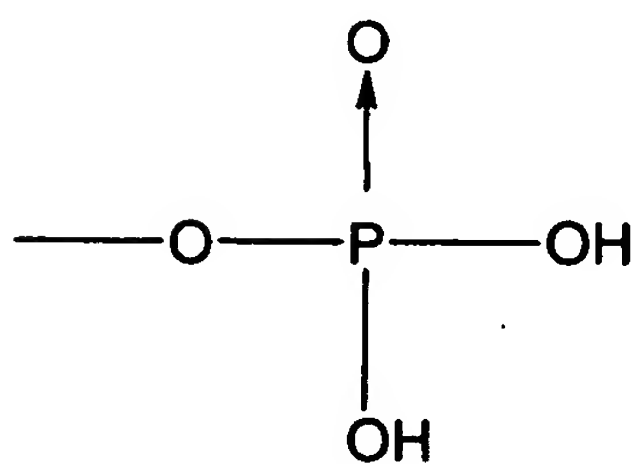
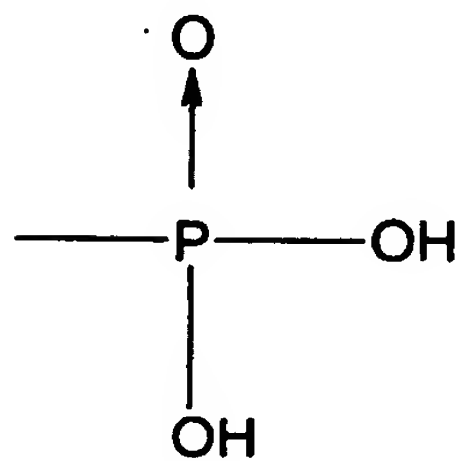
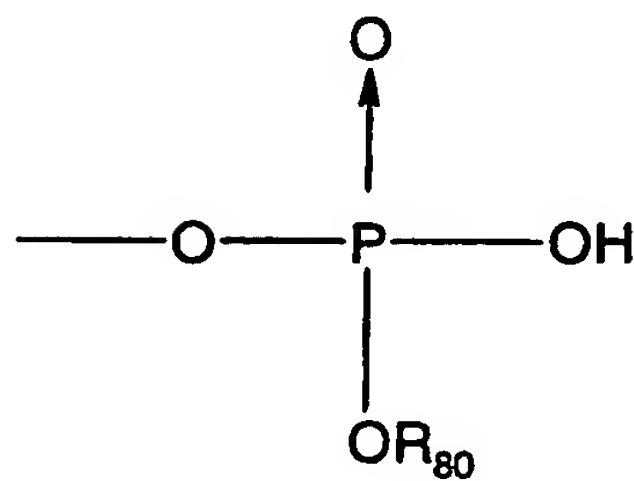
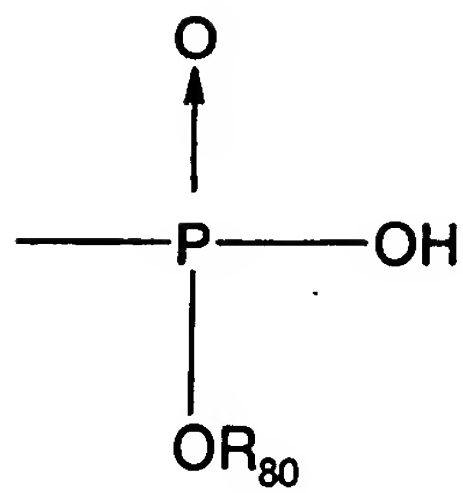
-5-tetrazolyl,

10

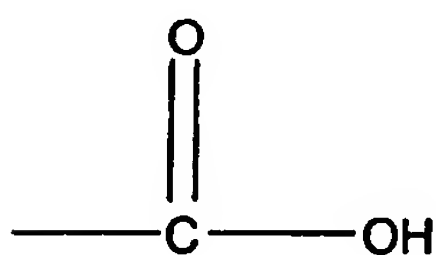
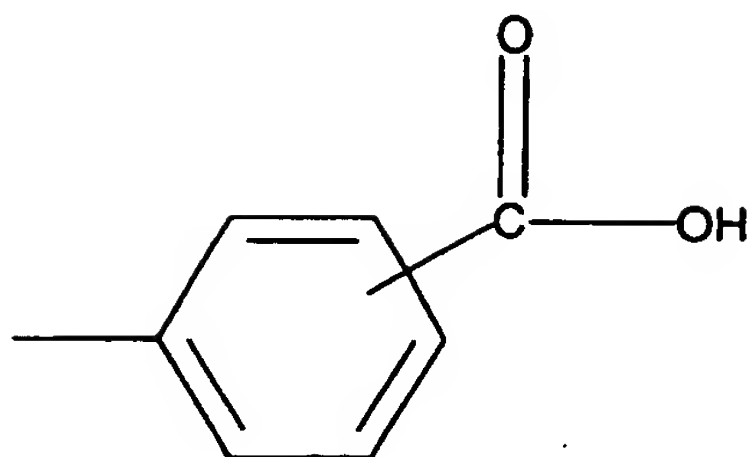
-SO₃H,



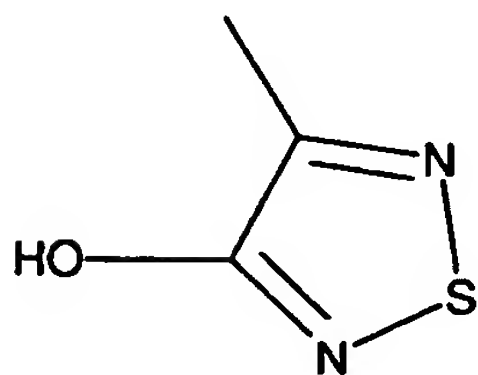
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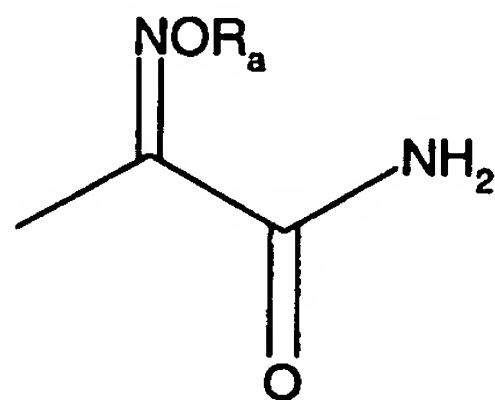


or



where R_{80} is a metal or C_1 - C_8 alkyl and R_{81} is an organic substituent or $-CF_3$.

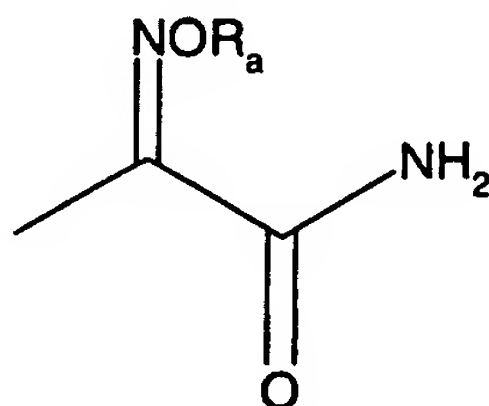
- 5 7. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



and the linking group $-(L_3)-$ is a bond; and R_a is
 10 hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

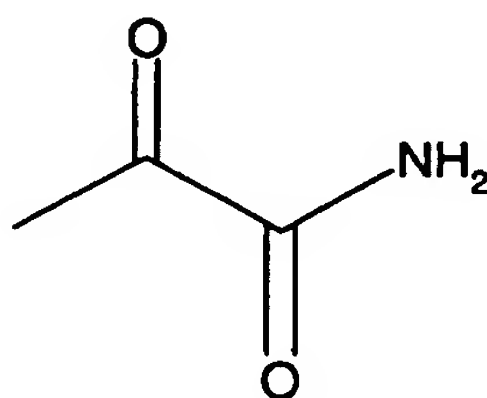
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8. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



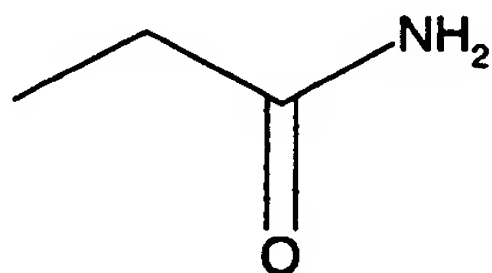
and the linking group $-(L_3)-$ is a bond; and R_a is
5 hydrogen.

9. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



10 and the linking group $-(L_3)-$ is a bond.

10. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



15 and the linking group $-(L_3)-$ is a bond.

11. The compound of Claim 1 wherein, for R_6 the non-interfering substituent is hydrogen, C_1 - C_8 alkyl,

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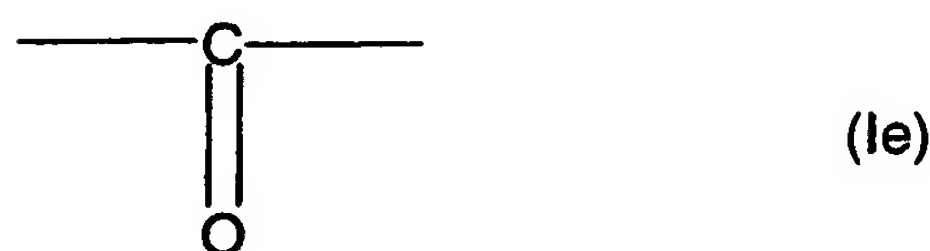
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C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈ alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

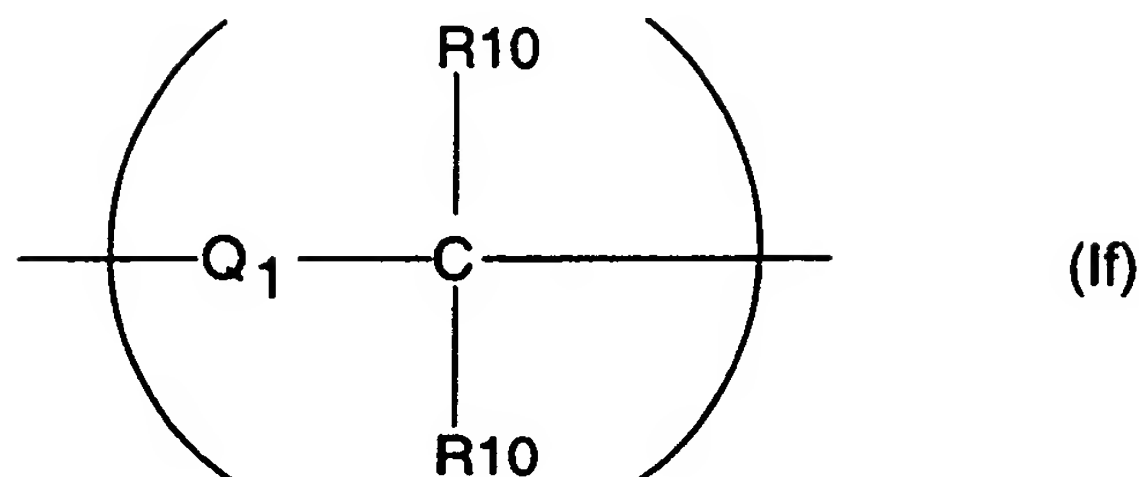
12. The compound of Claim 1 wherein for R₁ the divalent linking group -(L₁)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):

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or



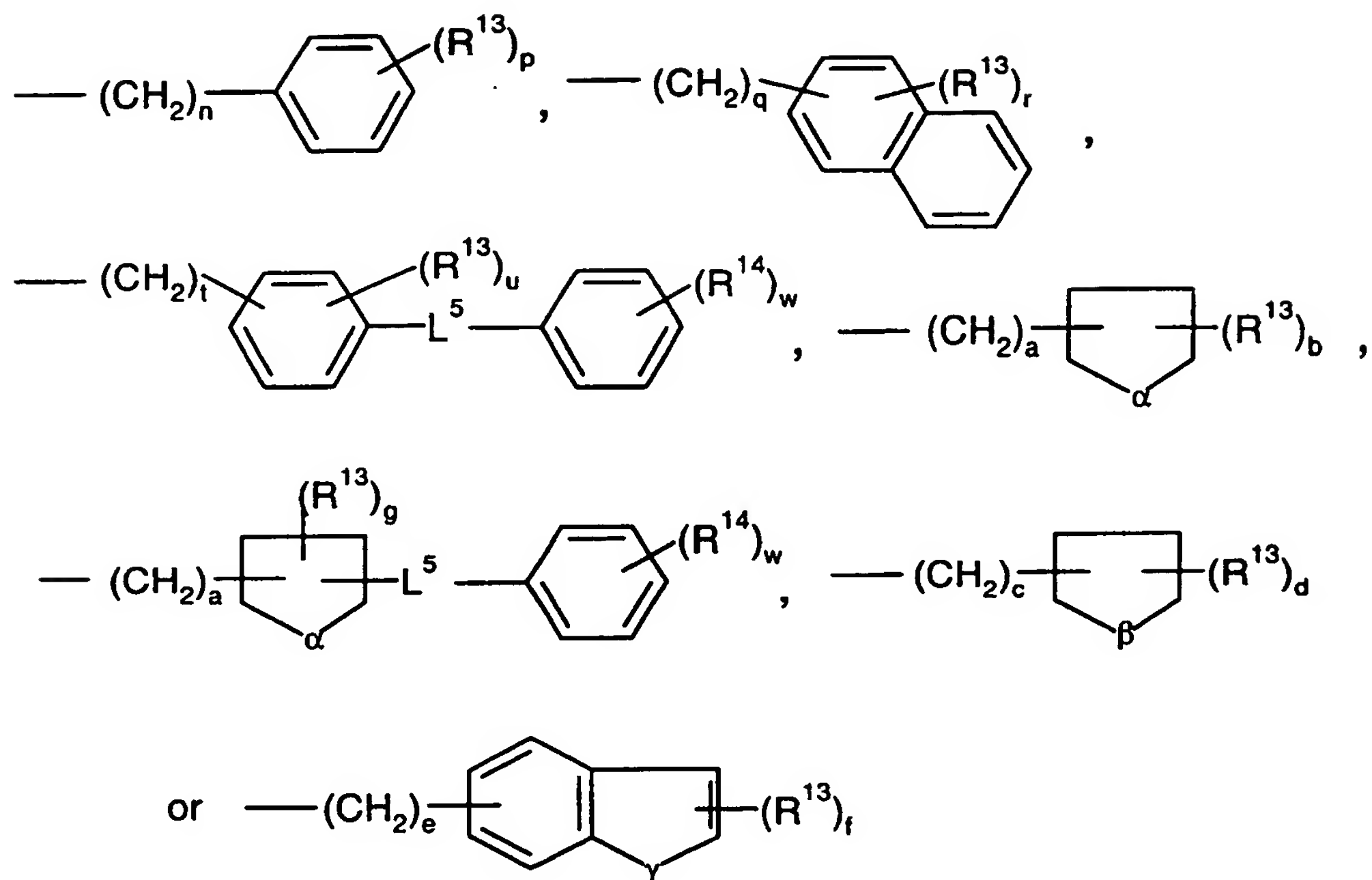
5 where Q_1 is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R_{10} is independently -H, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

13. The compound of claim 1 wherein the linking
10 group $-(\text{L}_1)\text{--}$ of R_1 is $-(\text{CH}_2)\text{--}$ or $-(\text{CH}_2\text{--CH}_2)\text{--}$.

14. The compound of claim 1 wherein the linking
group $-(\text{L}_{11})\text{--}$ of R_{11} is a bond and R_{11} is $-(\text{CH}_2)_m\text{--R}^{12}$
wherein m is an integer from 1 to 6, and R^{12} is a group
15 represented by the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8

5 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $\text{---}(\text{CH}_2)_v\text{---}$,

---C=C--- , ---CC--- , ---O--- , or ---S--- , v is an integer from 0 to 2, β is $\text{---CH}_2\text{---}$ or $\text{---}(\text{CH}_2)_2\text{---}$, γ is an oxygen atom or a sulfur

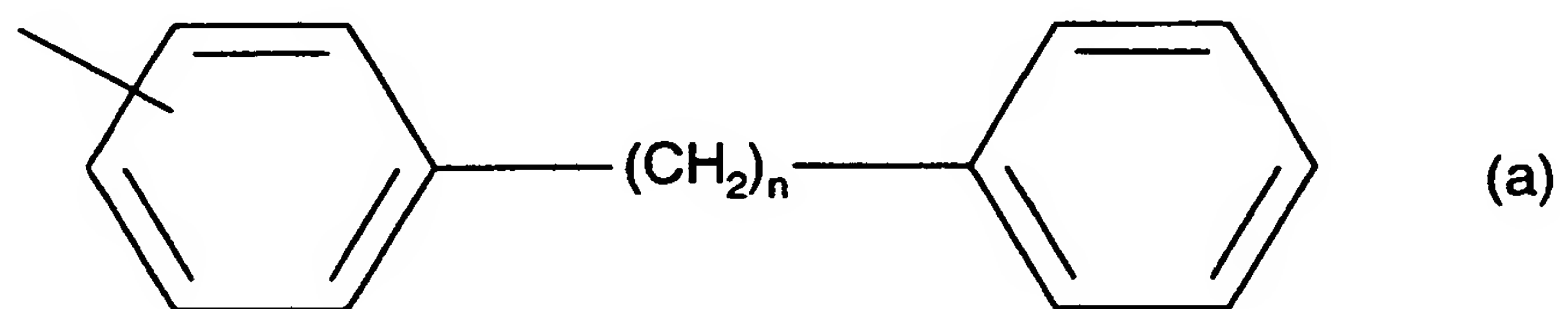
10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group

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consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen..

15. The compound of claim 1 wherein for R₁ the
5 group R₁₁ is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xlenyl, indenyl, stilbenyl, terphenyl,
10 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):



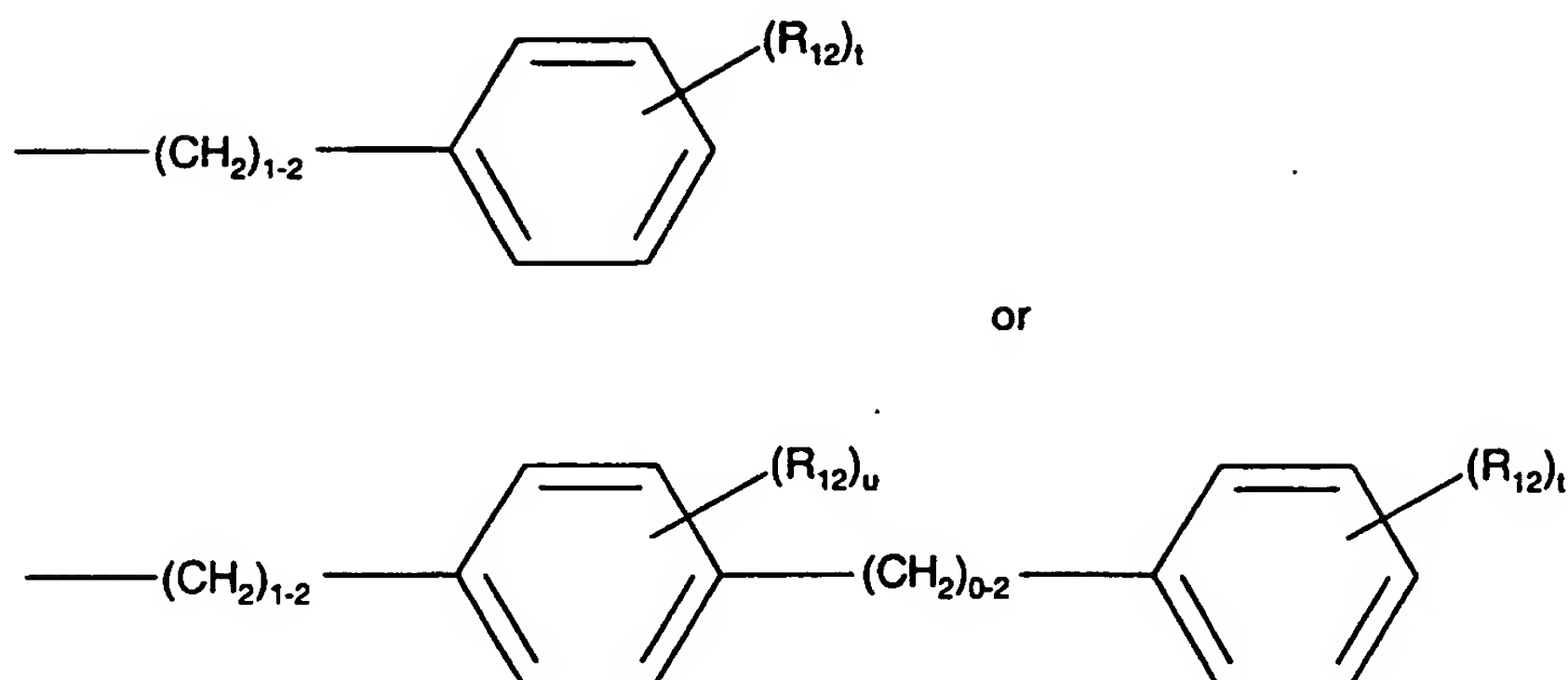
where n is a number from 1 to 8.

15

16. The compound of Claim 12 wherein for R₁ the combined group $-(L_1)-R_{11}$ is selected from the groups;

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where R_{12} is a radical independently selected from halo, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, $-S-(C_1-C_{10} \text{ alkyl})$, and C_1 -
 5 C_{10} haloalkyl, C_1 - C_{10} hydroxyalkyl and t is a number from 0 to 5 and u is a number from 0 to 4.

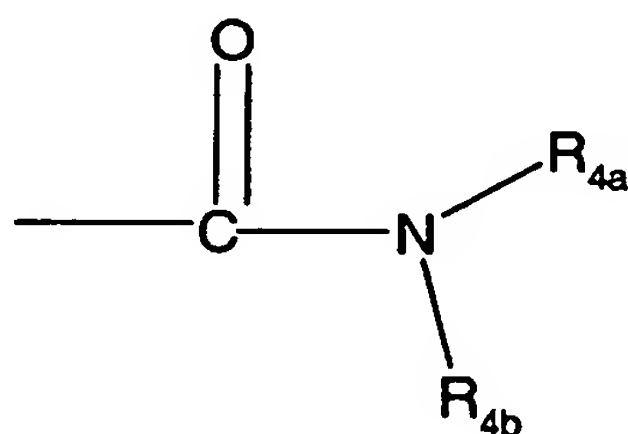
17. The compound of claim 1 wherein for R_1 the radical R_{11} is a substituted or unsubstituted
 10 heterocyclic radical selected from pyrrolyl, pyrrolodinyll, piperidinyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl,
 15 dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1.2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl,
 20 pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl,

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quinazolinylmorpholino, thiomorpholino, homopiperazinyl,
tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-
dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-
5 dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny,
hexamethyleneiminium, heptamethyleneiminium, piperazinyl
or quinoxaliny.

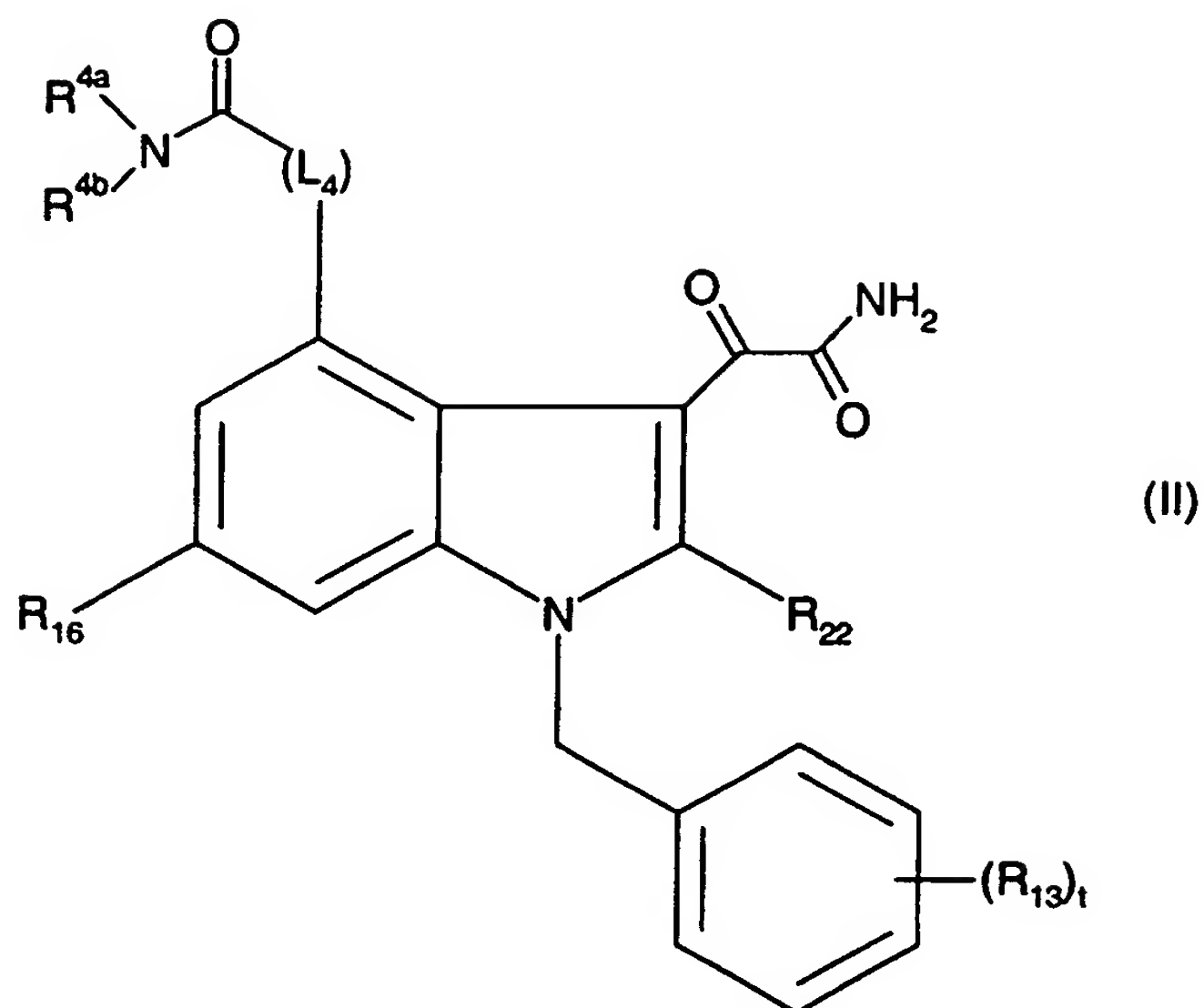
18. The compound of claim 1 wherein R₄ is the
10 group, -(L_C)-(acylamino acid group) and wherein the
(acylamino acid group) is:



15 and R^{4a} is selected from the group consisting of H, (C₁-
C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein
NR^{4b} is an amino acid residue with the nitrogen atom being
part of the amino group of the amino acid.

20 19. An indole compound represented by the
formula (II), or a pharmaceutically acceptable salt,
solvate, or prodrug derivative thereof;

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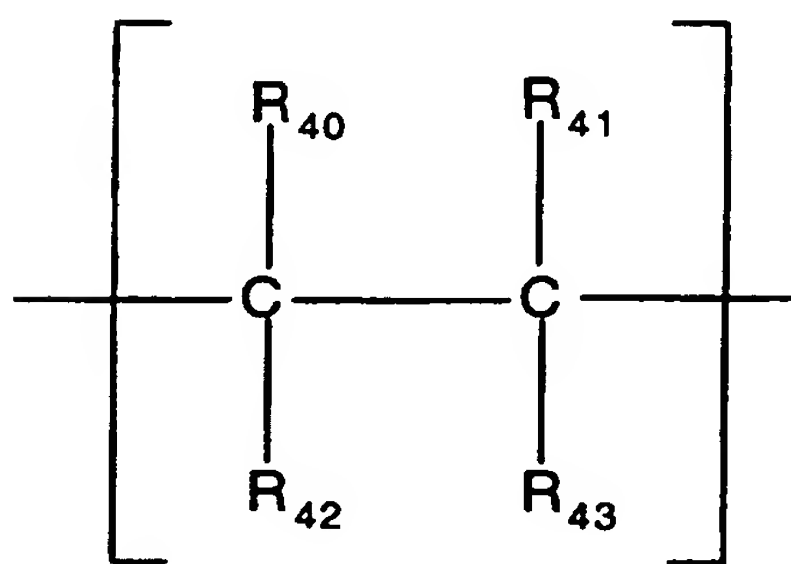
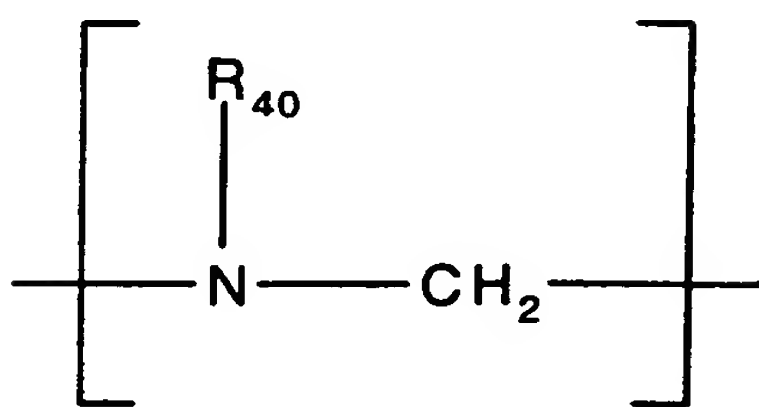
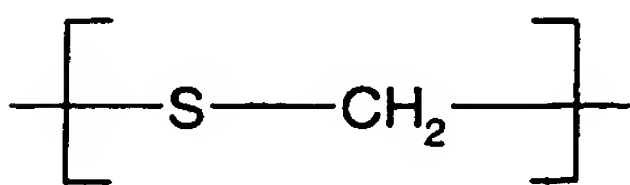
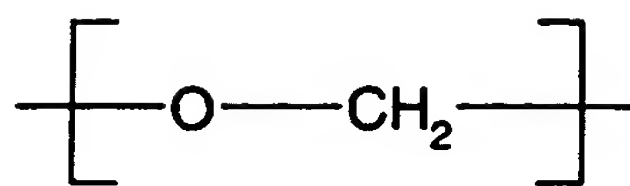
5 wherein ;

R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃;

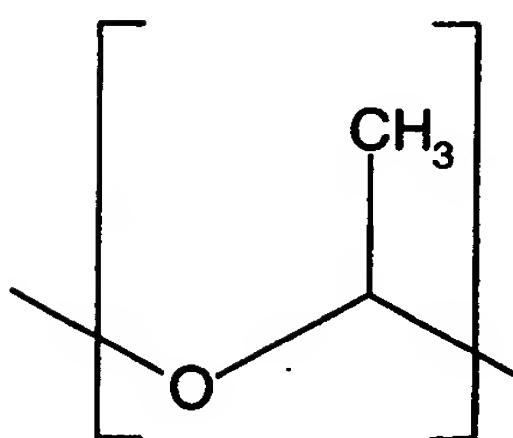
R^{4a} is hydrogen; and

10 NR^{4b} is an amino acid residue with the nitrogen atom being part of the amino group of the amino acid, and -
(L_C)- is a divalent group selected from;

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or



5 where R₄₀, R₄₁, R₄₂, and R₄₃ are each independently selected from hydrogen or C₁-C₈ alkyl.

R₁₆ is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, and halo.

10

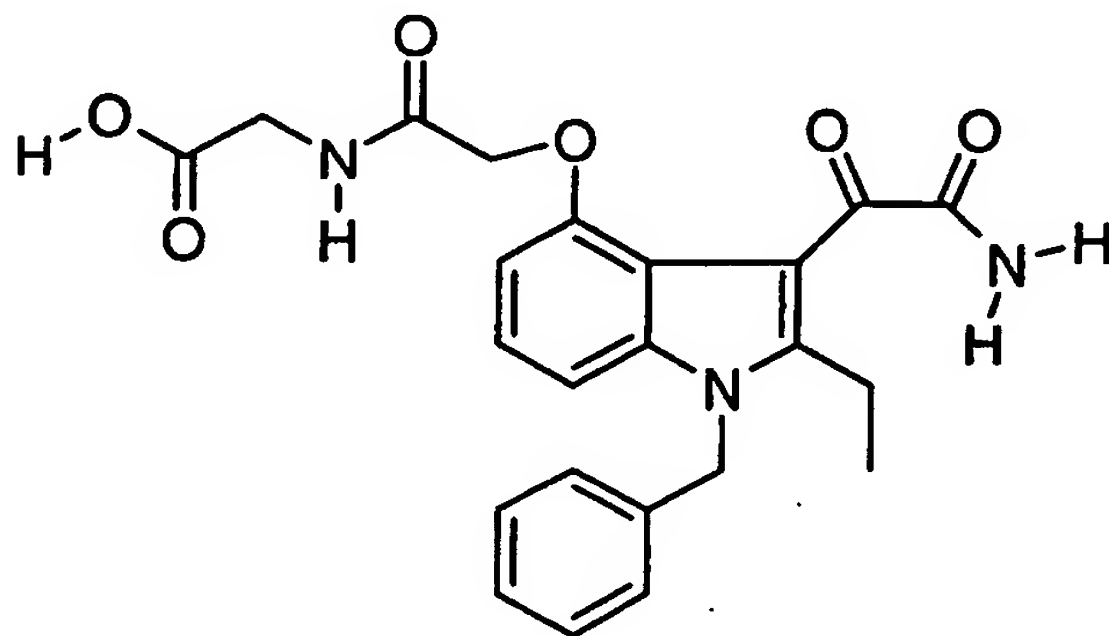
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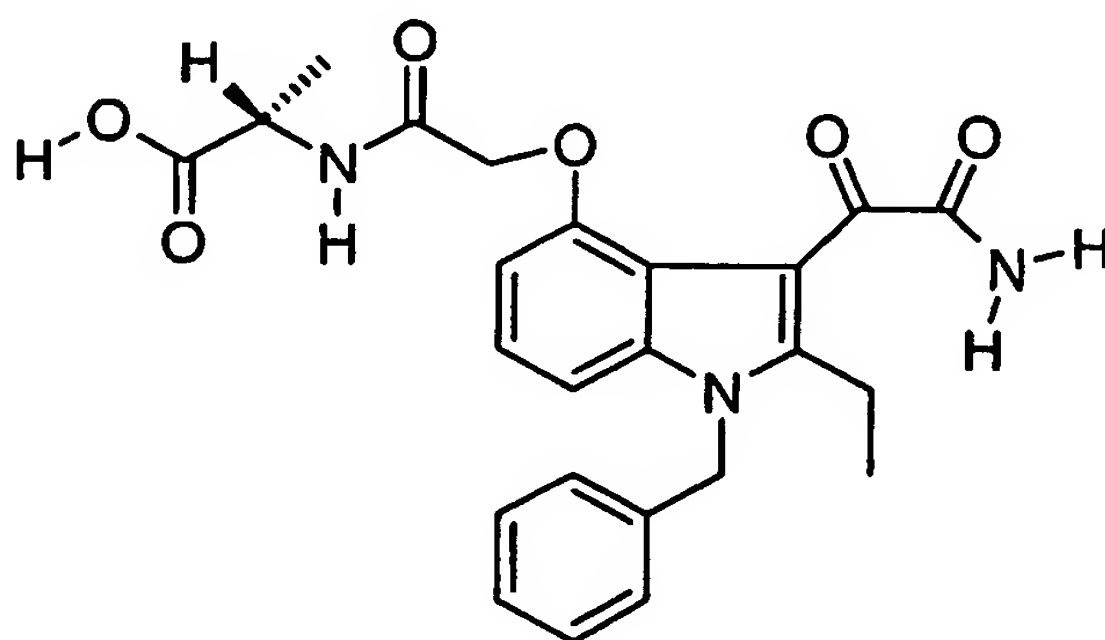
R_{13} is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, phenyl, halophenyl, and halo, and t is an integer from 0 to 5.

5

20. An indole compound represented by the formulae (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9), (C10) or (C11);



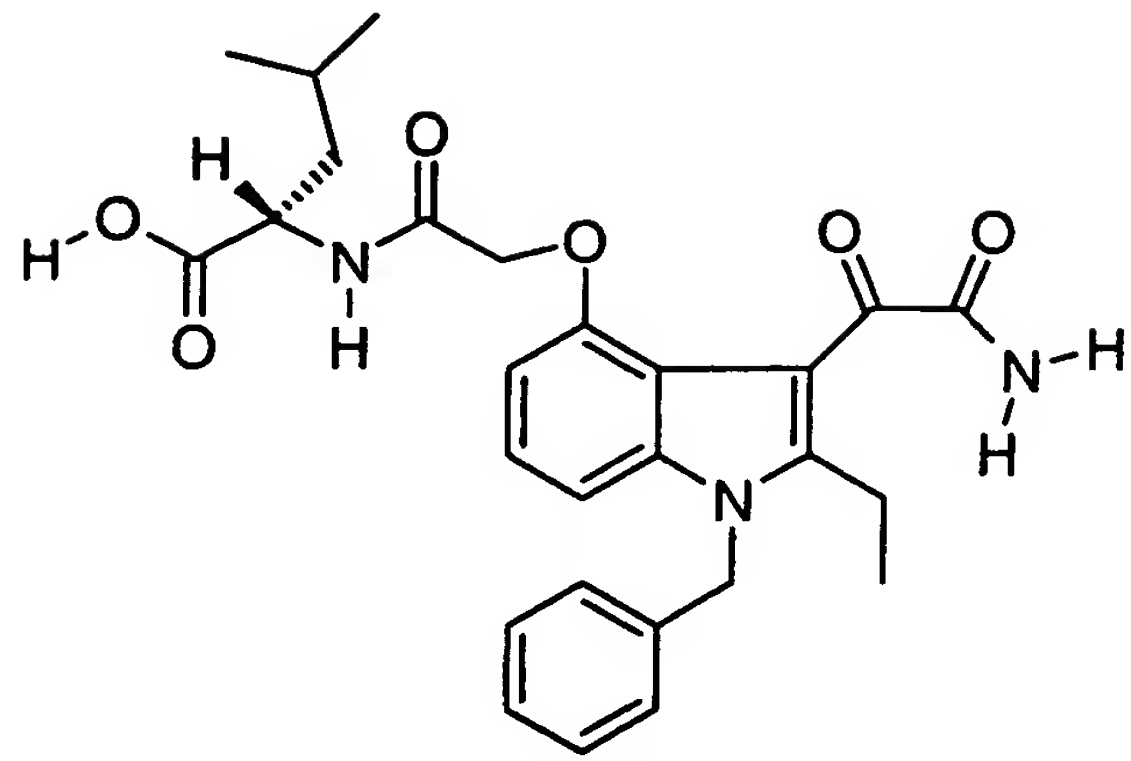
(C1),



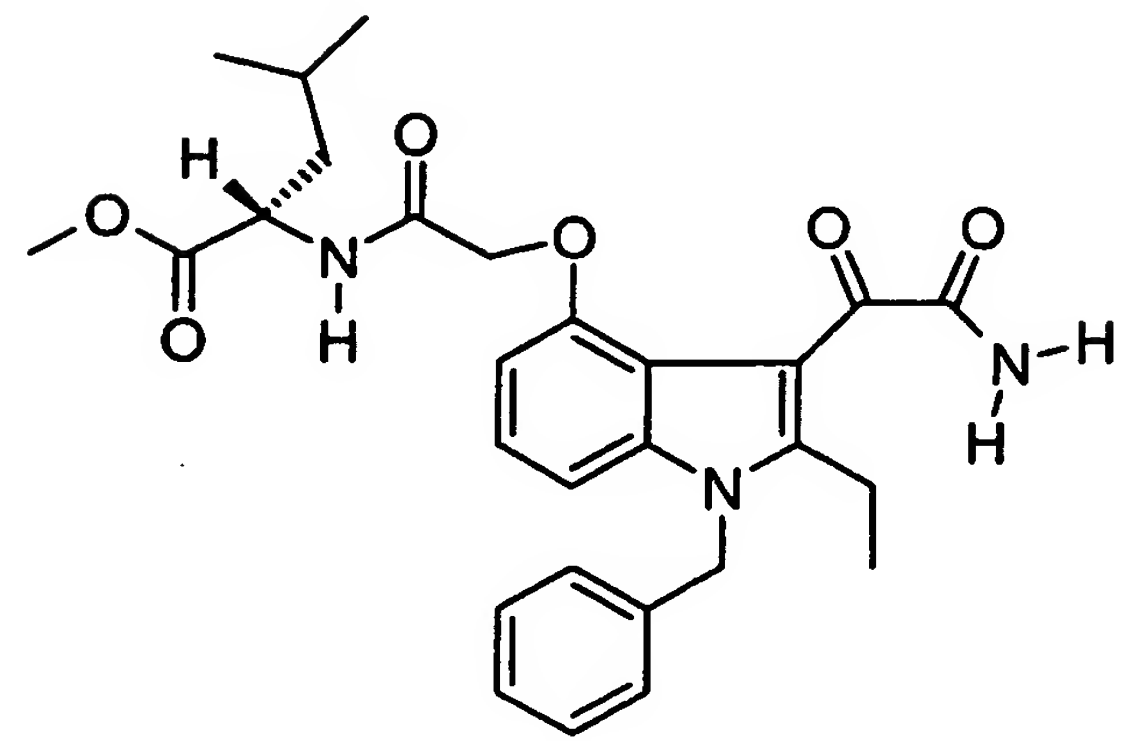
(C2),

10

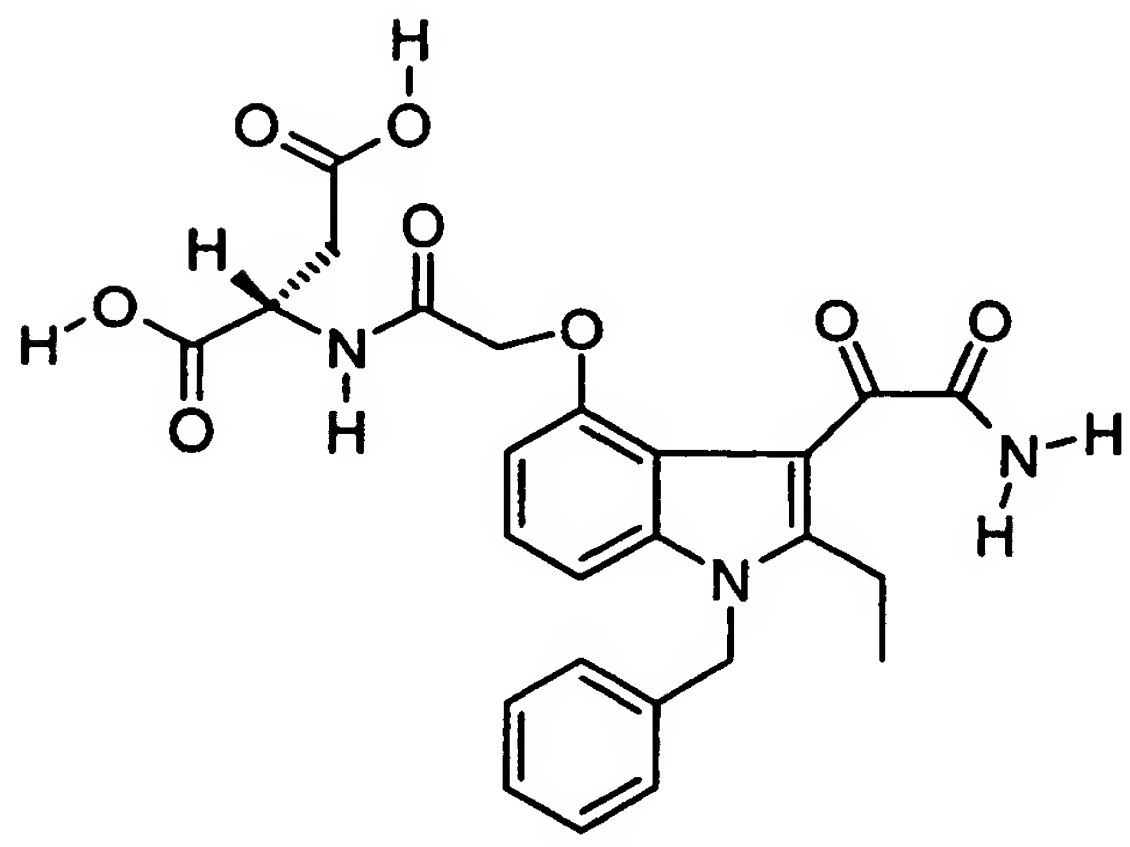
-130-



(C3) ,

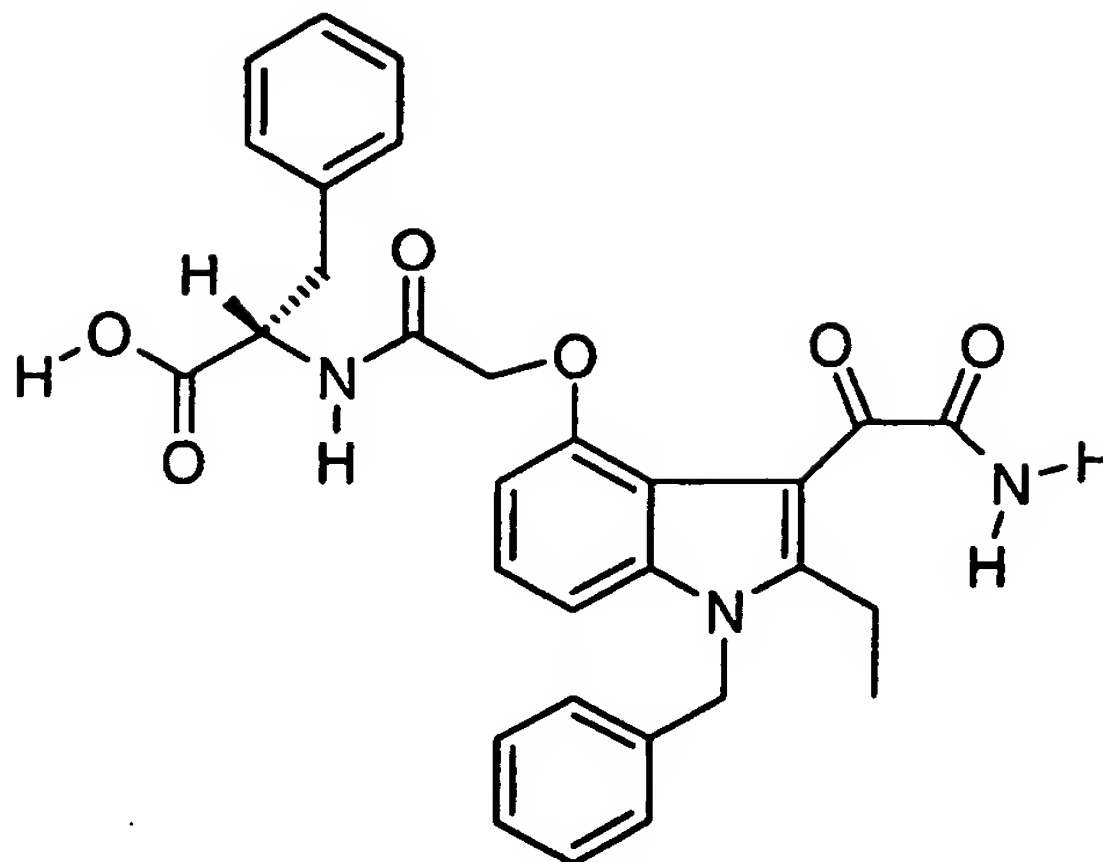


(C4) ,

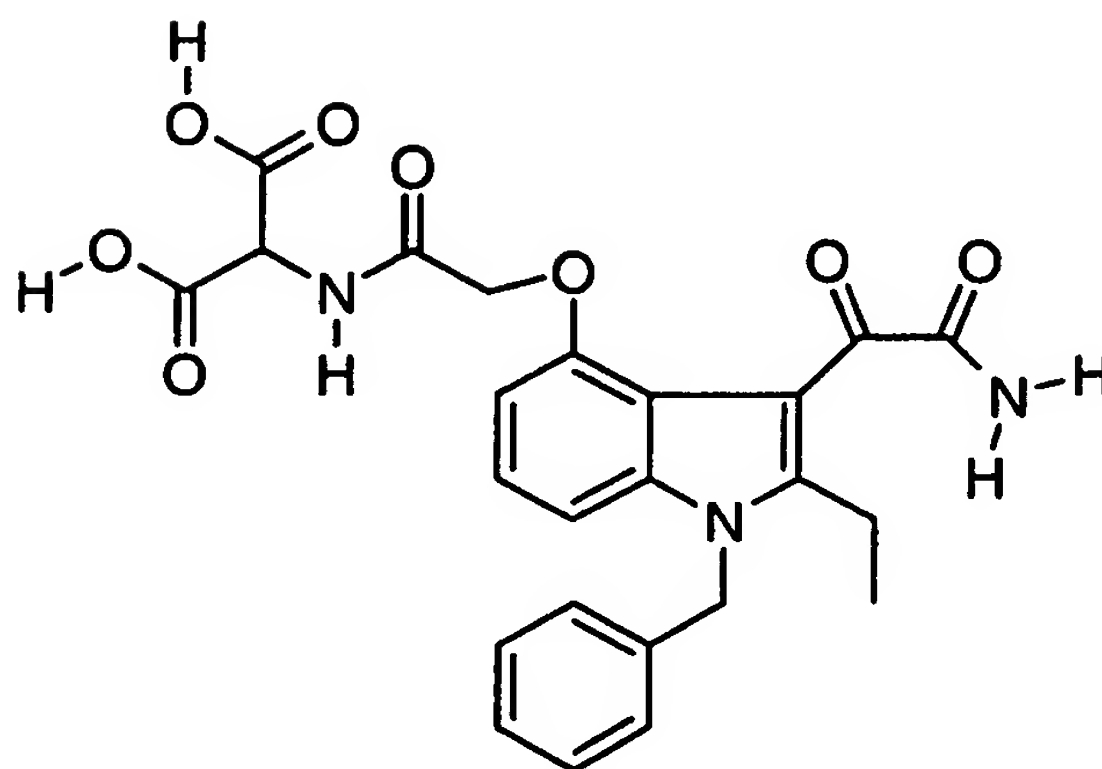


(C5) ,

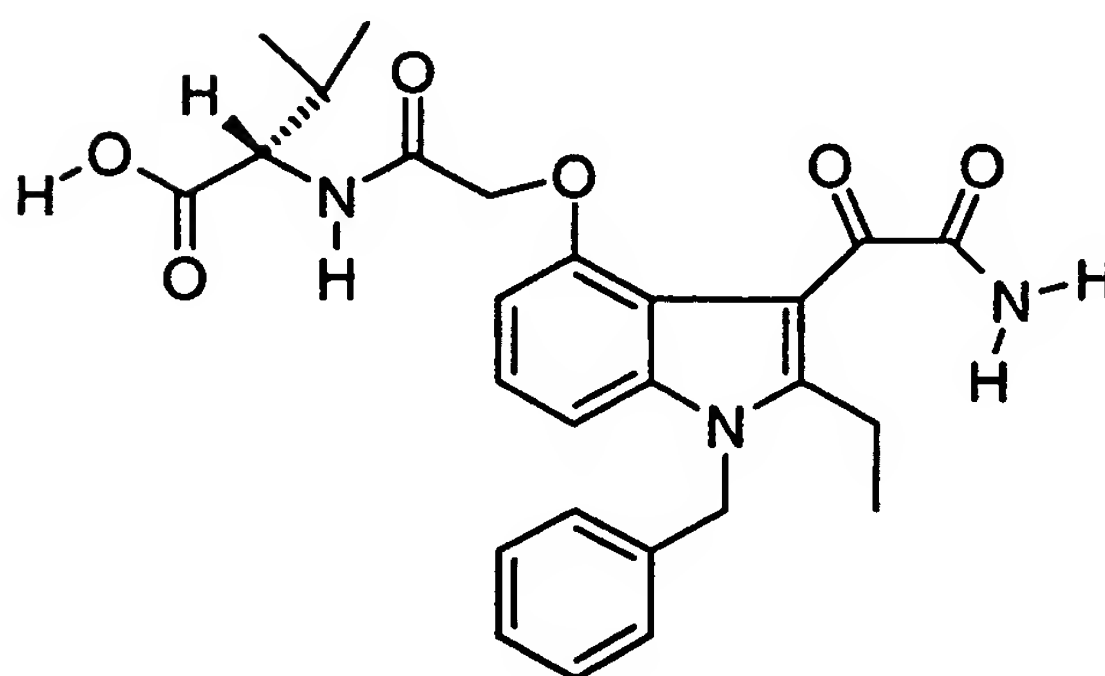
-131-



(C6) ,



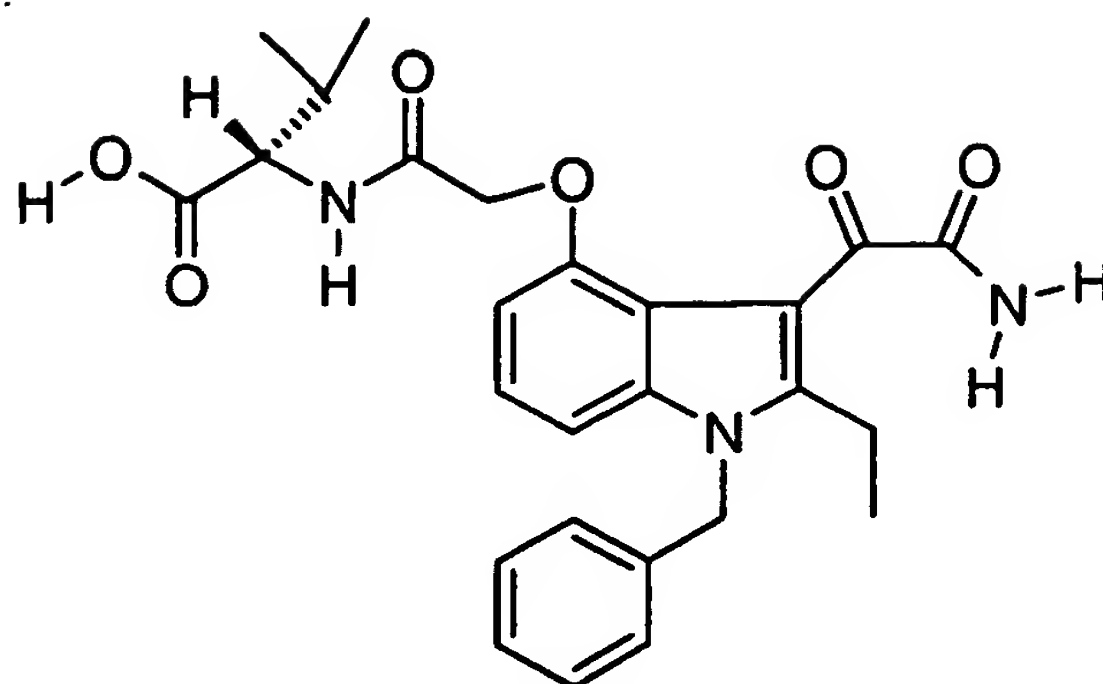
(C7) ,



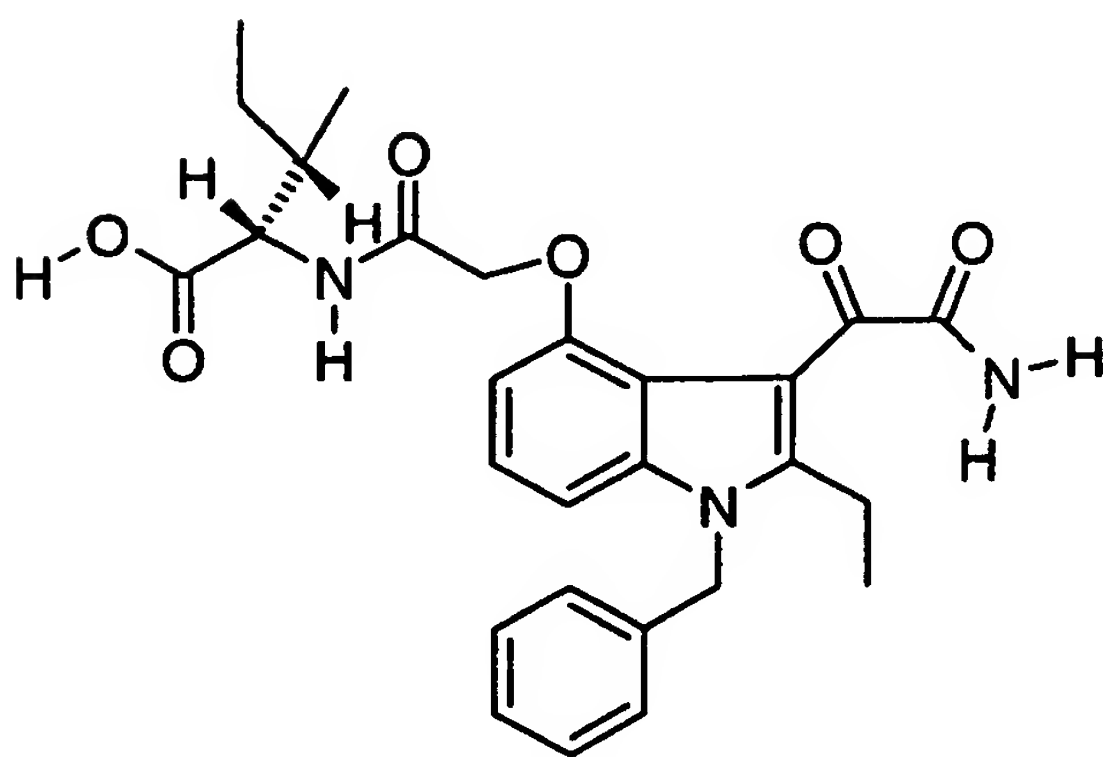
(C8) ,

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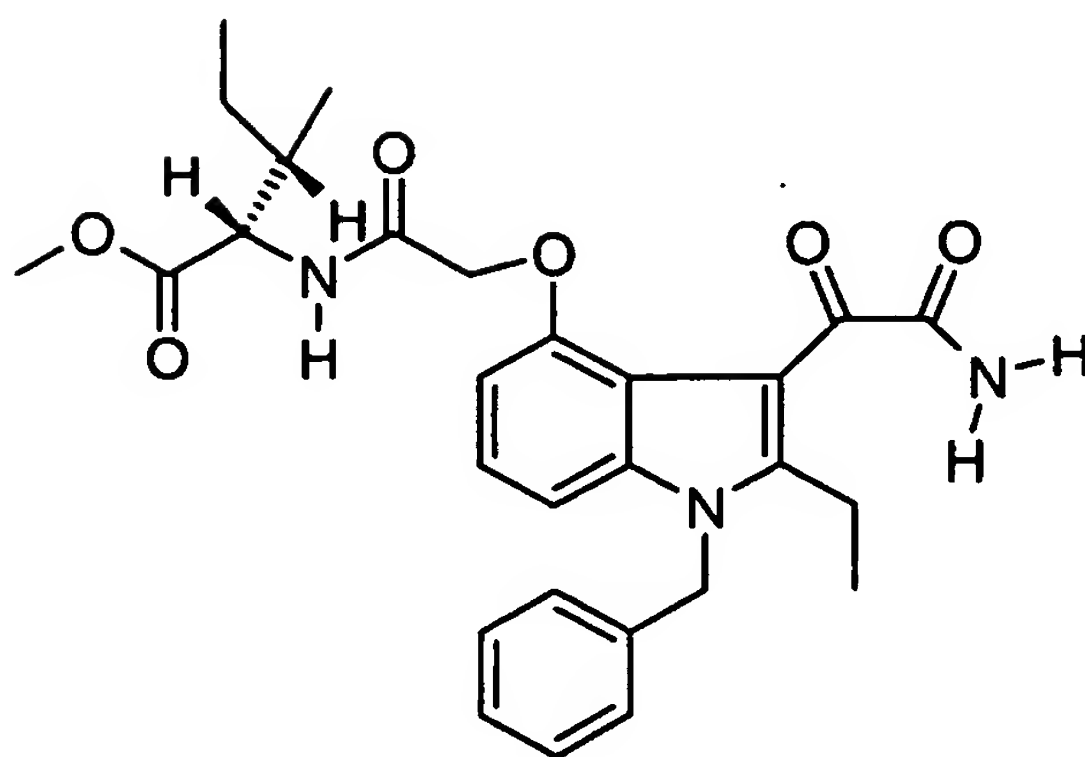
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(C9) ,



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.

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20. A compound of claim 1 selected from the group consisting of:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

15 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-valine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-valine;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

21. A pharmaceutical formulation comprising a indole compound as claimed in claim 1 together with a
10 pharmaceutically acceptable carrier or diluent therefor.

22. A method of inhibiting sPLA₂ mediated release of fatty acid which comprises contacting sPLA₂ with a therapeutically effective amount of indole compound as
15 claimed in claim 1.

23. A method of treating a mammal, including a human, to alleviate the pathological effects of Inflammatory Diseases; wherein the method comprises
20 administration to said mammal of at least one indole compound as claimed in Claim 1 in a pharmaceutically effective amount.

24. A compound of claim 1 or a pharmaceutical
25 formulation containing an effective amount of the

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compound of claim 1 in treatment of Inflammatory Diseases.

25. A compound of claim 1 or a pharmaceutical
5 formulation containing an effective amount of the
compound of claim 1 for use as an inhibitor for
inhibiting sPLA₂ mediated release of fatty acid.

26. Use of a pharmaceutical composition comprising
10 sPLA₂ inhibitor compounds according to Claim 1 and
mixtures thereof for the manufacture of a medicament for
the therapeutic treatment of Inflammatory Diseases.

SPLA2 INHIBITORS

Field of the Invention

This invention relates to novel indole compounds
5 useful for Inflammatory Diseases.

Background of the Invention

The structure and physical properties of human non-
pancreatic secretory phospholipase A₂ (hereinafter
10 called, "sPLA₂") has been thoroughly described in two
articles, namely, "Cloning and Recombinant Expression of
Phospholipase A₂ Present in Rheumatoid Arthritic
Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski,
Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.;
15 Kloss, Jean; and Johnson, Lorin K.; The Journal of
Biological Chemistry, Vol. 264, No. 10, Issue of April
5, pp. 5335-5338, 1989; and "Structure and Properties of
a Human Non-pancreatic Phospholipase A₂" by Kramer, Ruth
M.; Hession, Catherine; Johansen, Berit; Hayes,
20 Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard,
Richard; and Pepinsky, R. Blake; The Journal of
Biological Chemistry, Vol. 264, No. 10, Issue of April
5, pp. 5768-5775, 1989; the disclosures of which are
incorporated herein by reference.

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It is believed that sPLA₂ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA₂ mediated release
5 of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA₂; such as sepsis or rheumatoid arthritis.

10 It is desirable to develop new compounds and treatments for sPLA₂ induced diseases.

Summary of the Invention

This invention provides novel indole compounds
15 having potent and selective effectiveness as inhibitors of mammalian sPLA₂.

This invention is also the use of novel indole compounds useful in the treatment and prevention of
20 Inflammatory Diseases.

This invention is also the use of novel of indole compounds to inhibit mammalian sPLA₂ mediated release of fatty acids.

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This invention is also a pharmaceutical composition containing any of the indole compounds of the invention.

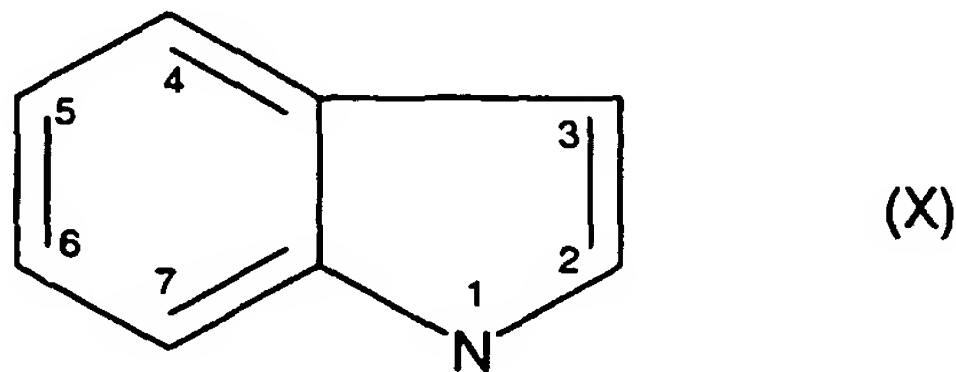
5 **I. Definitions:**

 The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma,
10 allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy,
15 enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease,
20 arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism,
25 bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing),

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miscellaneous forms of arthritis, neuropathic joint
disease (charco and joint), hemarthrosis (hemarthrosic),
Henoch-Schonlein Purpura, hypertrophic osteoarthropathy,
multicentric reticulohistiocytosis, arthritis associated
5 with certain diseases, surcoilosis, hemochromatosis,
sickle cell disease and other hemoglobinopathries,
hyperlipoproteineimia, hypogammaglobulinemia,
hyperparathyroidism, acromegaly, familial Mediterranean
fever, Behat's Disease, systemic lupus erythrematosis,
10 or relapsing polychondritis and related diseases which
comprises administering to a mammal in need of such
treatment a therapeutically effective amount of the
compound of formula I in an amount sufficient to inhibit
sPLA₂ mediated release of fatty acid and to thereby
15 inhibit or prevent the arachidonic acid cascade and its
deleterious products.

The term, "indole nucleus" refers to a nucleus
(having numbered positions) with the structural
20 formula (X):



The indole compounds of the invention employ
certain defining terms as follows:

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The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary
5 butyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated
10 number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group
15 containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or
20 unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodiny, piperidinyl, furanyl,
25 thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl,

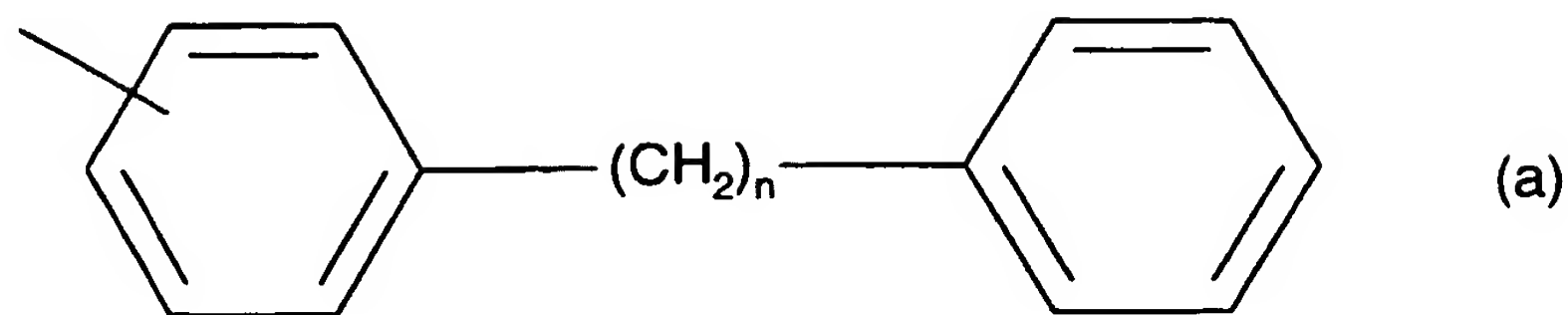
-6-

indolyl, carbazolyl, norharmanyl, azaindolyl,
benzofuranyl, dibenzofuranyl, dibenzothiophenyl,
indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl,
anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl,
5 benzothiazolyl, purinyl, pyridinyl, dipyridyl,
phenylpyridinyl, benzylpyridinyl, pyrimidinyl,
phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,
phthalazinyl, quinazolinyl, morpholino, thiomorpholino,
homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl,
10 oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-
dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidyl,
hexamethyleneiminium, heptamethyleneiminium, piperazinyl
and quinoxalinyl.

15

The term, "carbocyclic radical" refers to radicals
derived from a saturated or unsaturated, substituted or
unsubstituted 5 to 14 membered organic nucleus whose ring
forming atoms (other than hydrogen) are solely carbon
20 atoms. Typical carbocyclic radicals are cycloalkyl,
cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl,
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
indenyl, stilbenyl, terphenyl, diphenylethylenyl,
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
25 biphenyl, bibenzyl and related bibenzyl homologues
represented by the formula (a):

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where n is a number from 1 to 8.

5 The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4,5,6 and/or 7 of the indole nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the

10 heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈

15 alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈

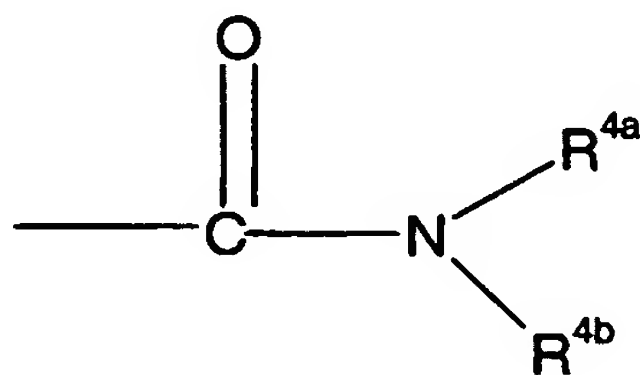
20 alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino,

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bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$,
chloro, cyano, cyanoguanidiny, fluoro, guanidino,
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,
iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl,
5 and carbonyl; where n is from 1 to 8 and R is C_1-C_8
alkyl.

The term, "organic substituent" refers to a
monovalent radical consisting of carbon and hydrogen
10 with or without oxygen, nitrogen, sulfur, halogen, or
other elements. Illustrative organic substituents are
 C_1-C_8 alkyl, aryl, C_7-C_{14} aralkyl, C_7-C_{14} alkaryl, C_3-C_8
cycloalkyl, C_1-C_8 alkoxyalkyl and these groups
substituted with halogen, $-CF_3$, $-OH$, C_1-C_8 alkyl, amino,
15 carbonyl, and $-CN$.

The term, "acylamino acid group" is represented by
the formula:



20

wherein R^{4a} is selected from the group consisting of H,
(C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl, $-CF_3$;
and wherein NR^{4b} is an amino acid residue of either a

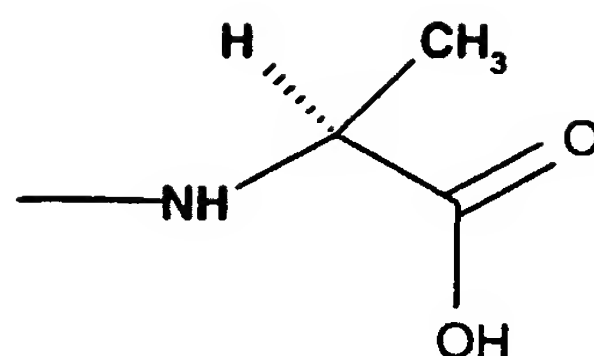
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natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A typical amino acid is selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, 5 glycine, asparagine, cysteine, glutamine, glutamic acid, histidine, lysine, methionine, serine, threonine, tryptophan, tyrosine and derivatives thereof. Also contemplated within the definition of amino acid is *l*-proline, *d*-proline and derivatives thereof. Also 10 contemplated within the definition of amino acids are peptides, polypeptides and derivatives thereof.

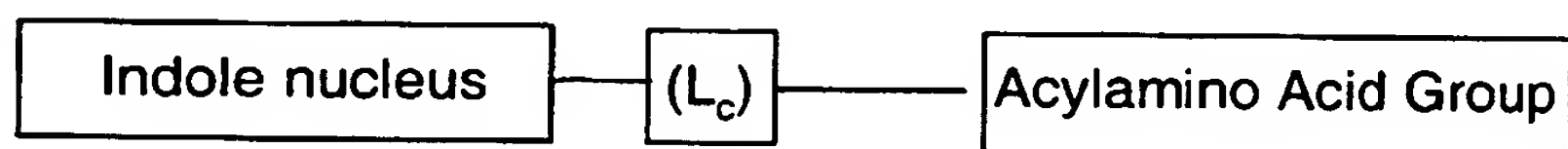
The term "substituted group" is an organic group substituted with one or more non-interfering 15 substituents.

The terms, "amino acid residue" refer to the portion of the amino acid group coupled at the nitrogen atom of the amino terminus. It is the amino acid less a 20 hydrogen atom from the amino terminus. It is further illustrated as used herein for the amino acid alanine attached at the nitrogen atom as shown below:

-10-

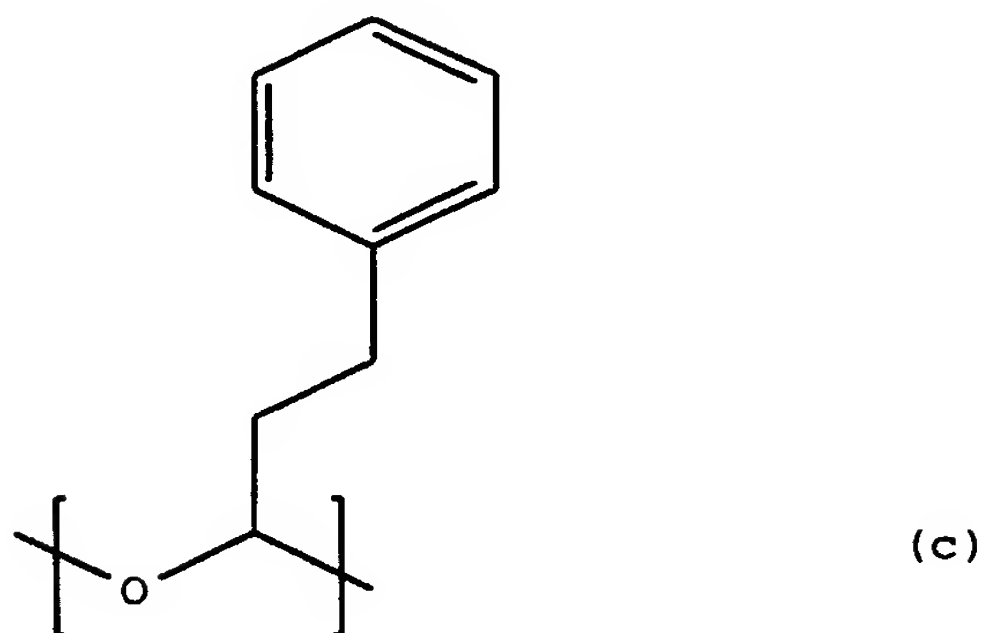
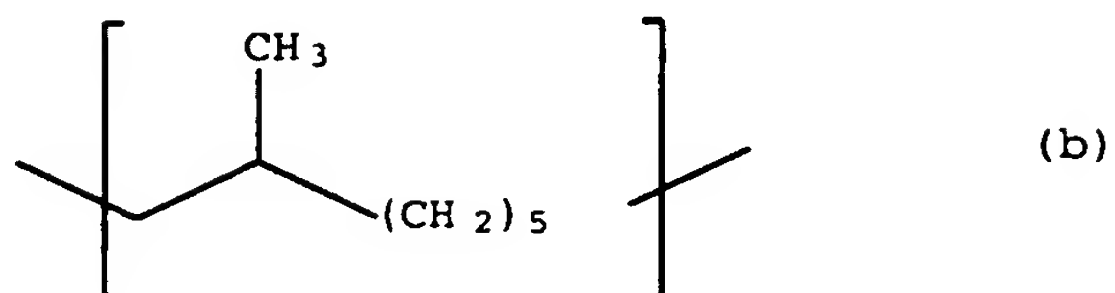
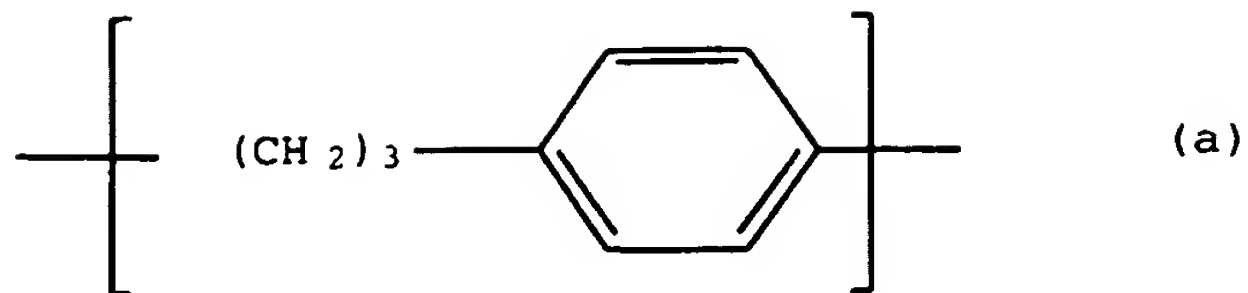


The words, "acylamino acid linker" refer to a divalent linking group symbolized as, $-(L_c)-$, which has the function of joining the 4 - position of the indole nucleus to an acylamino acid group in the general relationship:



The words, "acylamino acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group $-(L_c)-$ that connects the 4 - position of the indole nucleus with the acylamino acid group. The presence of a carbocyclic ring in $-(L_c)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_c)-$. Illustrative acylamino acid linker groups are;

-11-



wherein, groups (a), (b) and (c) have acid linker lengths of 5, 7, and 2, respectively.

5

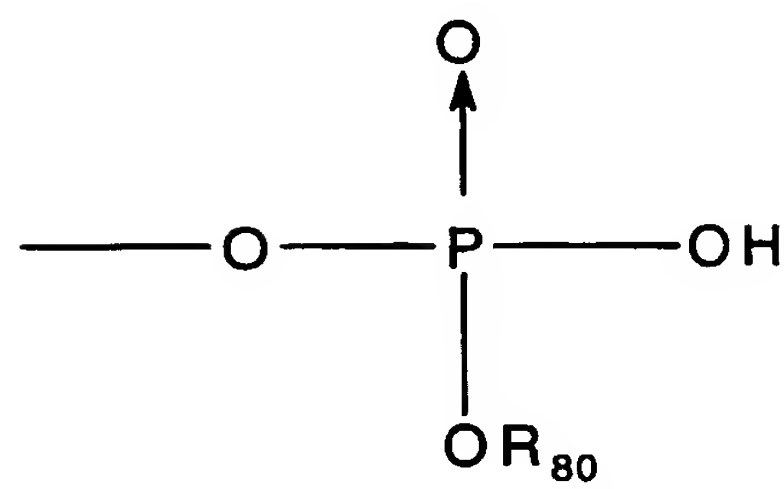
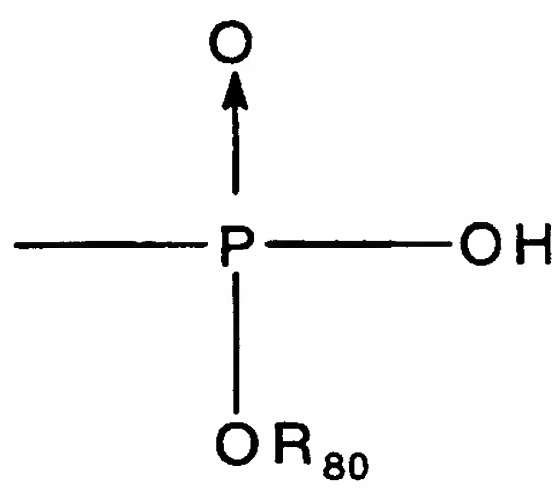
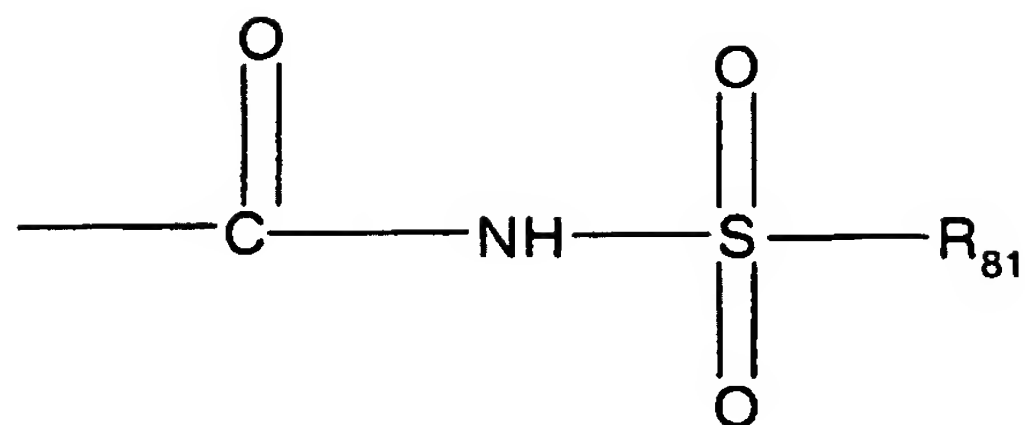
The term, "(acidic group)" means an organic group which when attached to an indole nucleus at position 5, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

10

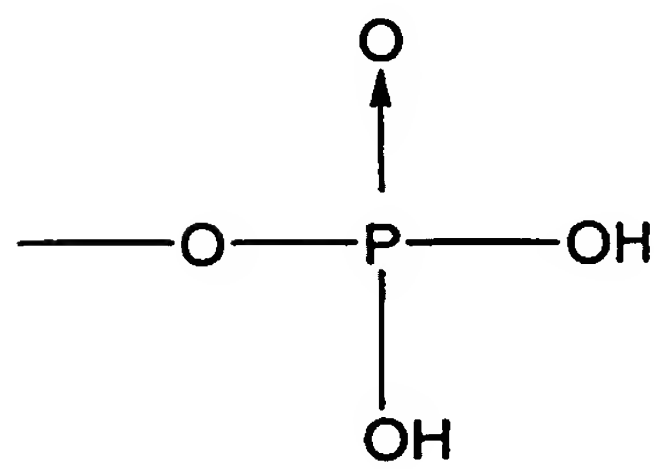
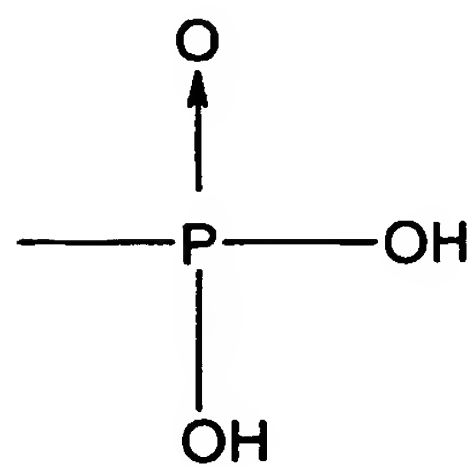
-5-tetrazolyl,

-SO₃H,

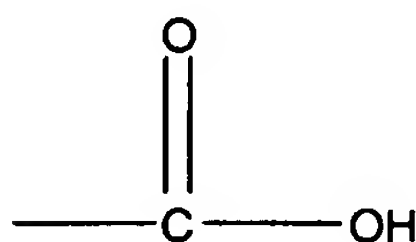
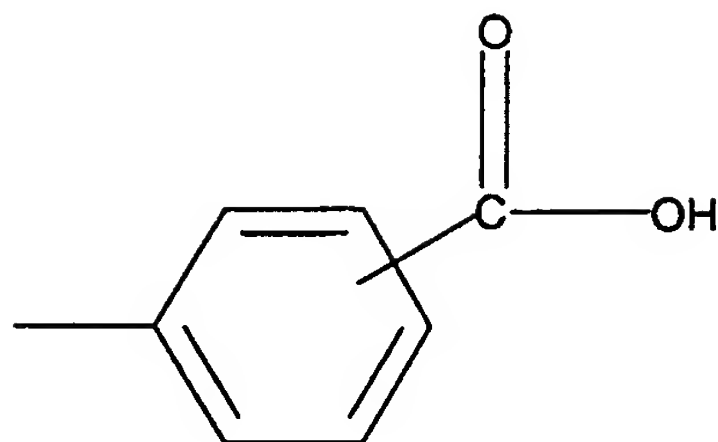
-12-



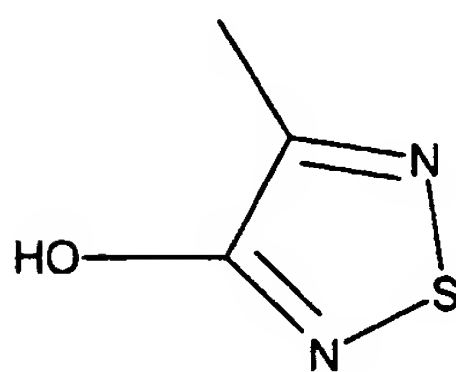
5



-13-

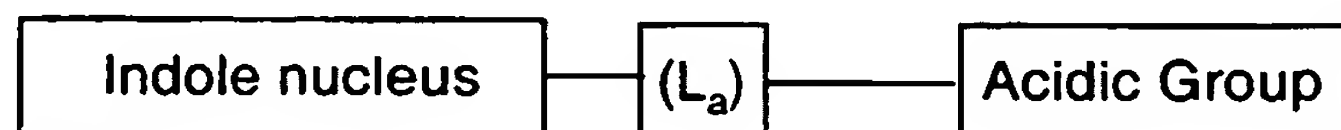


or



where n is 1 to 8, R_{g0} is a metal or C₁-C₈ and R_{g1}
 5 is an organic substituent or -CF₃.

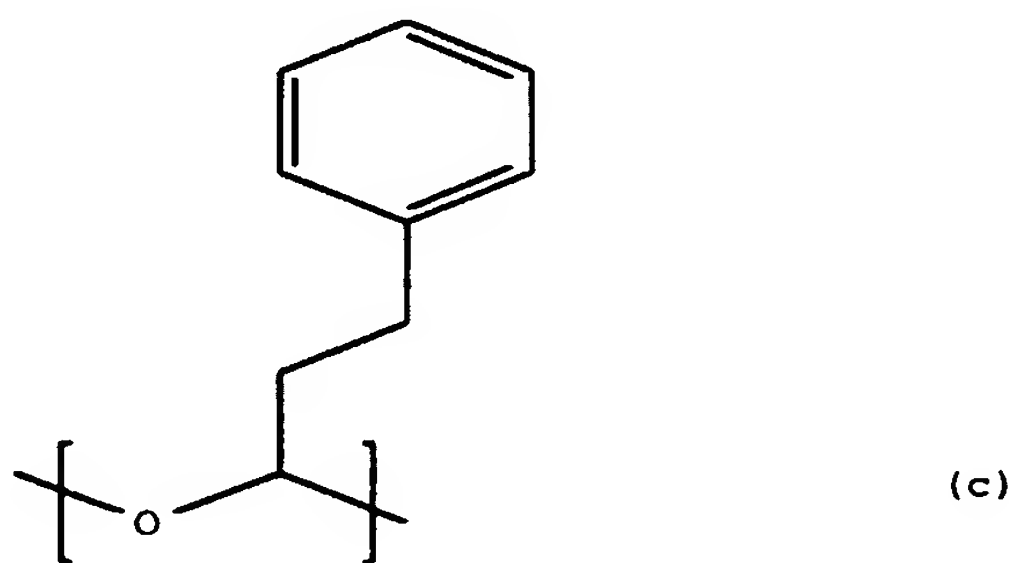
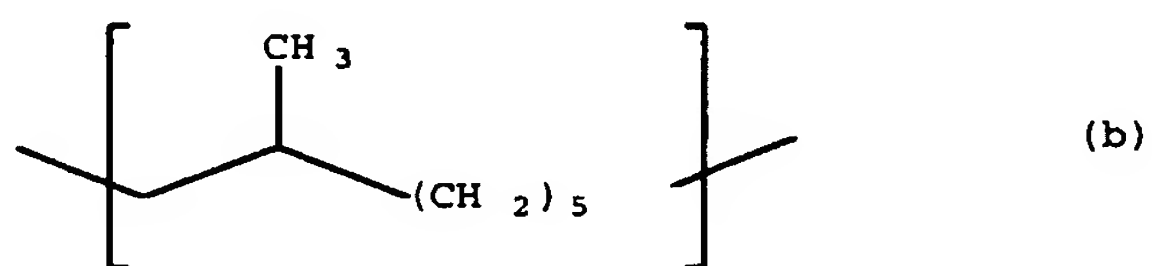
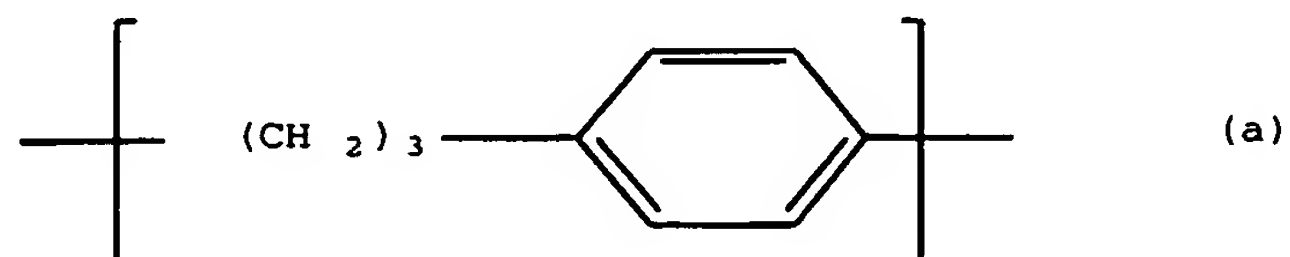
The words, "acid linker" refer to a divalent
 linking group symbolized as, -(L_a)-, which has the
 function of joining the 5 position of the indole nucleus
 10 to an acidic group in the general relationship:



The words, "acid linker length", refer to the number
 of atoms (excluding hydrogen) in the shortest chain of the
 15 linking group -(L_a)- that connects the 5 position of the

-14-

indole nucleus with the acidic group. The presence of a carbocyclic ring in $-(L_a)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in
5 the acid linker counts as 2 atoms in calculating the length of $-(L_a)-$. Illustrative acid linker groups are;



10 wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

-15-

The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals, $-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-$.

5

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_3$; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, and $-\text{CH}=\text{CH}_2$.

20

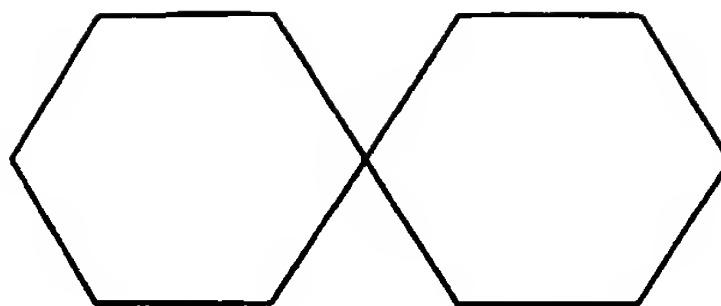
The term "oxime amide" means the radical,
 $-\text{C}=\text{NOR}-\text{C}(\text{O})\text{NH}_2$

The term "thio-oxime amide" means the radical
 $-\text{C}=\text{NOR}-\text{C}(\text{S})-\text{NH}_2$.

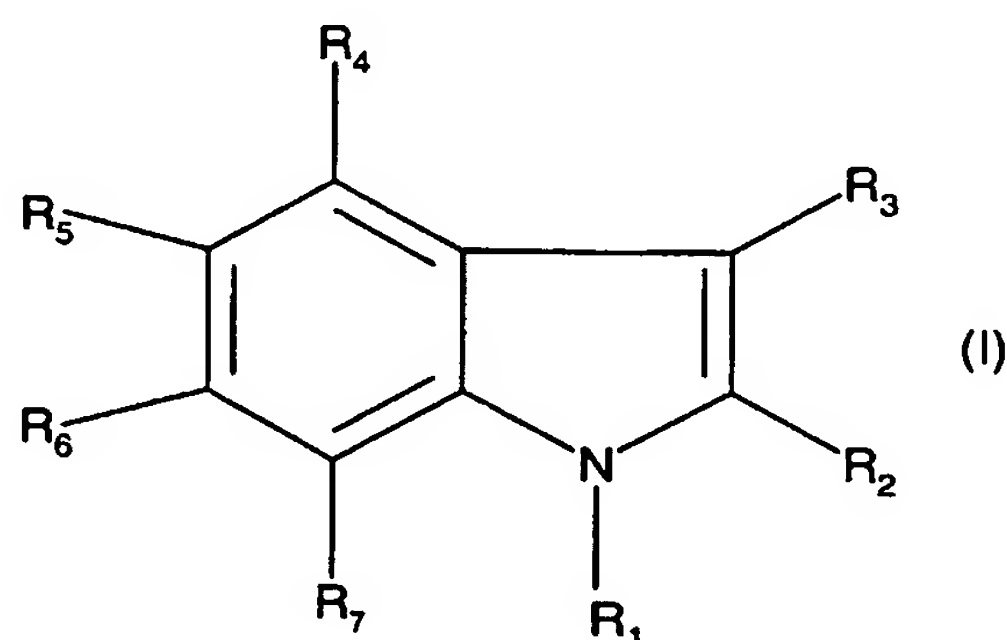
The term "spiro[5.5]undecanyl" refers to the group represented by the formula;

25

-16-

**II. The amino acid 1H-indole Compounds of the Invention:**

The present invention provides novel classes of
5 indole compounds useful as sPLA2 inhibitors for the
treatment of inflammation. Classes of indole compounds
of this invention include indole glyoxylamide amino acid
derivatives, indole-3-oxime amide amino acid derivatives
and indole acetamide amino acid derivatives. The
10 compounds of the invention have the general formula (I)
or a pharmaceutically acceptable salt, solvate or
prodrug thereof;



15

wherein ;

 R_1 is selected from groups (a), (b), and (c)

wherein;

-17-

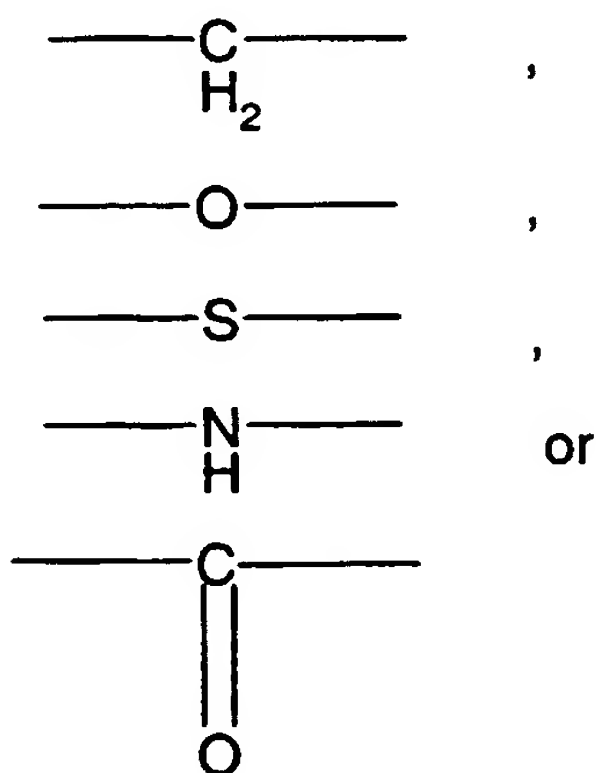
(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or
5 more independently selected non-interfering substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

10 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

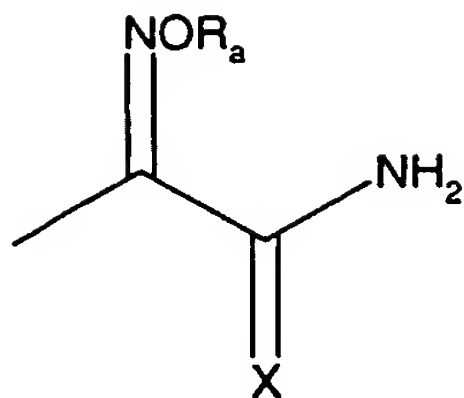
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:



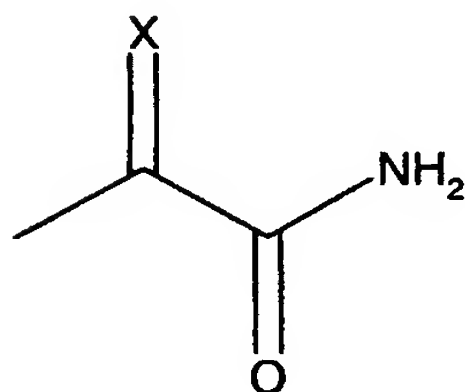
15

and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,

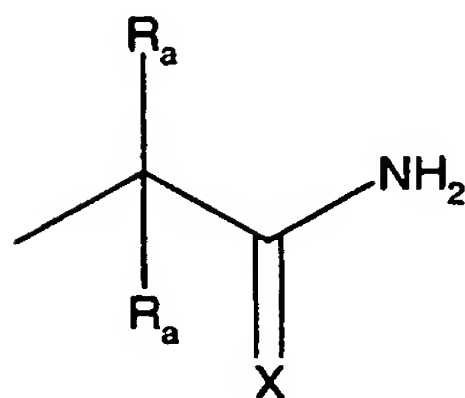
-18-



or



or



5

wherein X is oxygen or sulfur, R_a is independently selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

R_4 is the group, $-(L_C)-(acylamino\ acid\ group)$;

10 wherein $-(L_C)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein $-(L_a)-$, is an acid linker having an acid linker length

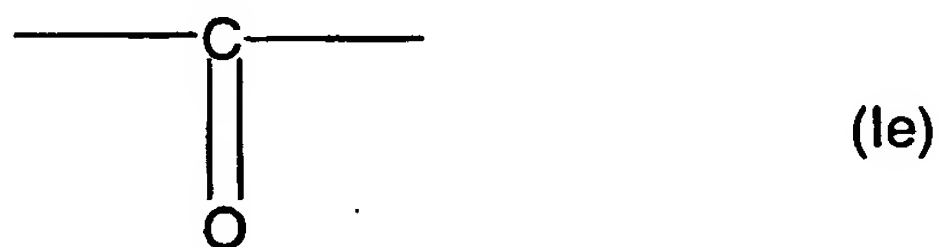
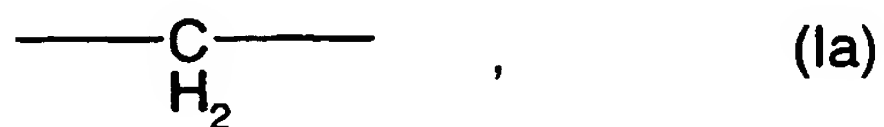
15 of 1 to 8.

-19-

R₆ and R₇ are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

Preferred Subgroups of Compounds of Formula (I):
Preferred R₁ substituents:

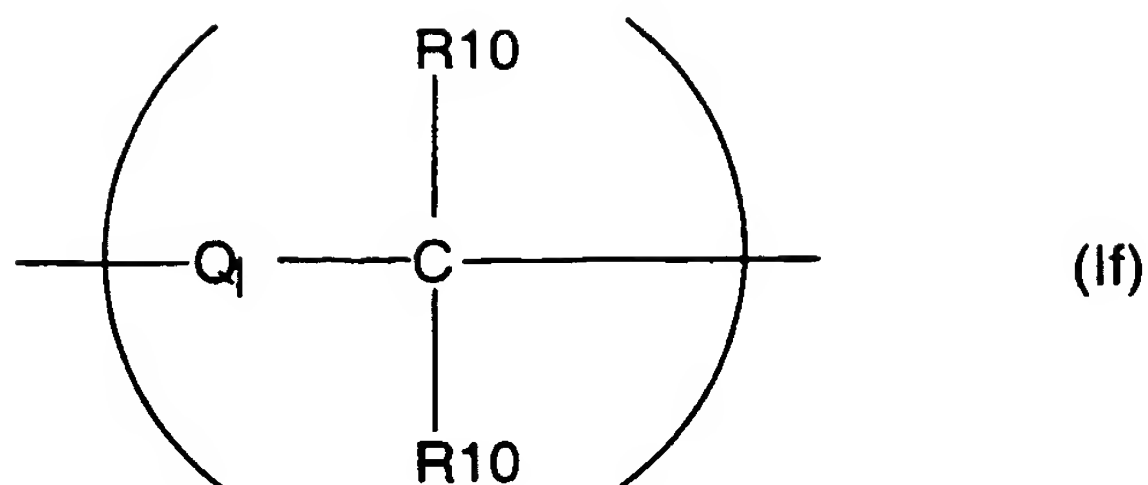
A preferred subclass of compounds of formula (I) are those where for R₁ the divalent linking group -(L₁)- is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



15

or

-20-

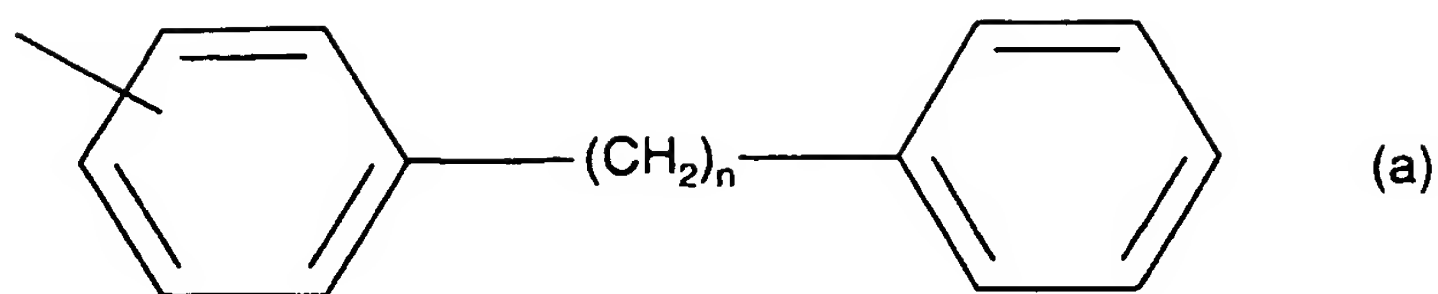


where Q_1 is a bond or any of the divalent groups (Ia), (Ib), (Ic), (Id), (Ie), and (If) and each R_{10} is
 5 independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

Particularly preferred as the linking group $-(L_1)-$ of
 R_1 is an alkylene chain of 1 or 2 carbon atoms, namely,
 10 $-(CH_2)-$ or $-(CH_2-CH_2)-$.

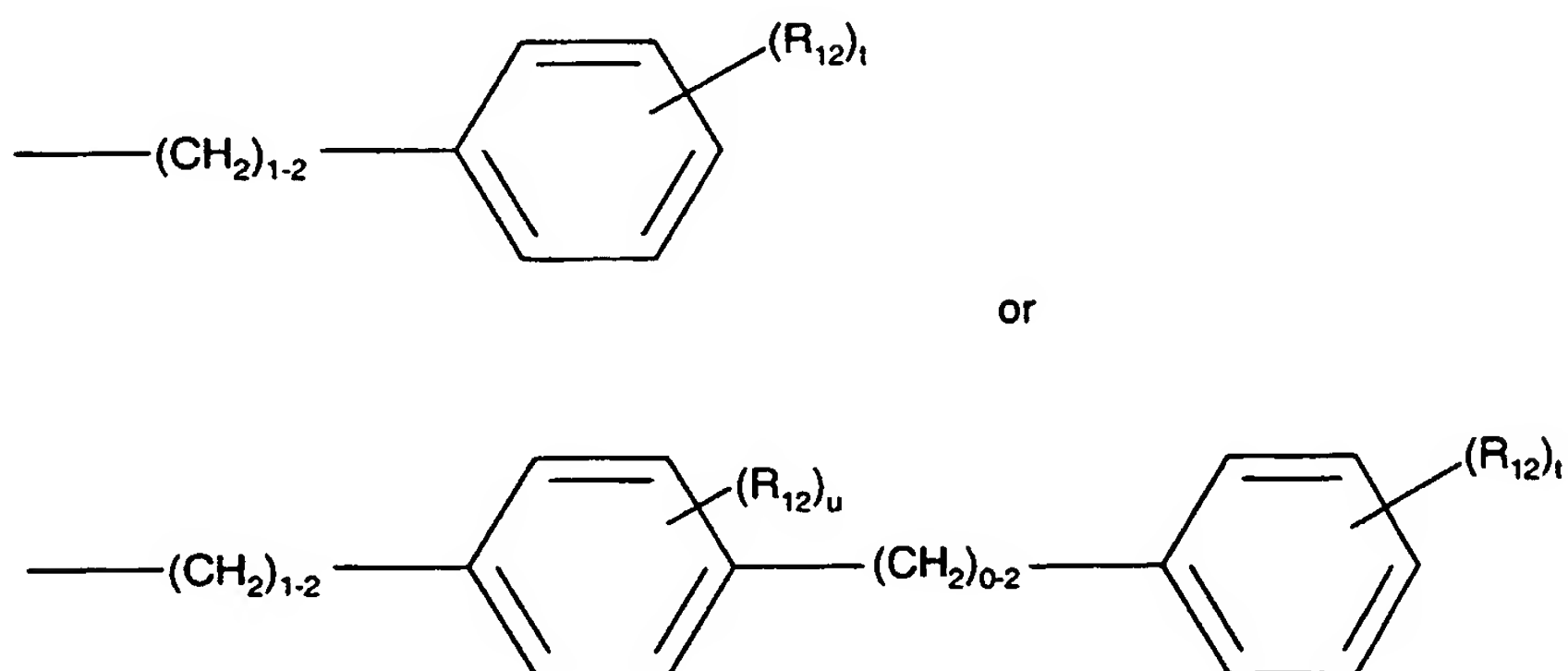
The preferred group for R_{11} is a substituted or unsubstituted group selected from the group consisting of C_5-C_{14} cycloalkyl, C_5-C_{14} cycloalkenyl, phenyl, naphthyl,
 15 norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a);

-21-



where n is a number from 1 to 8.

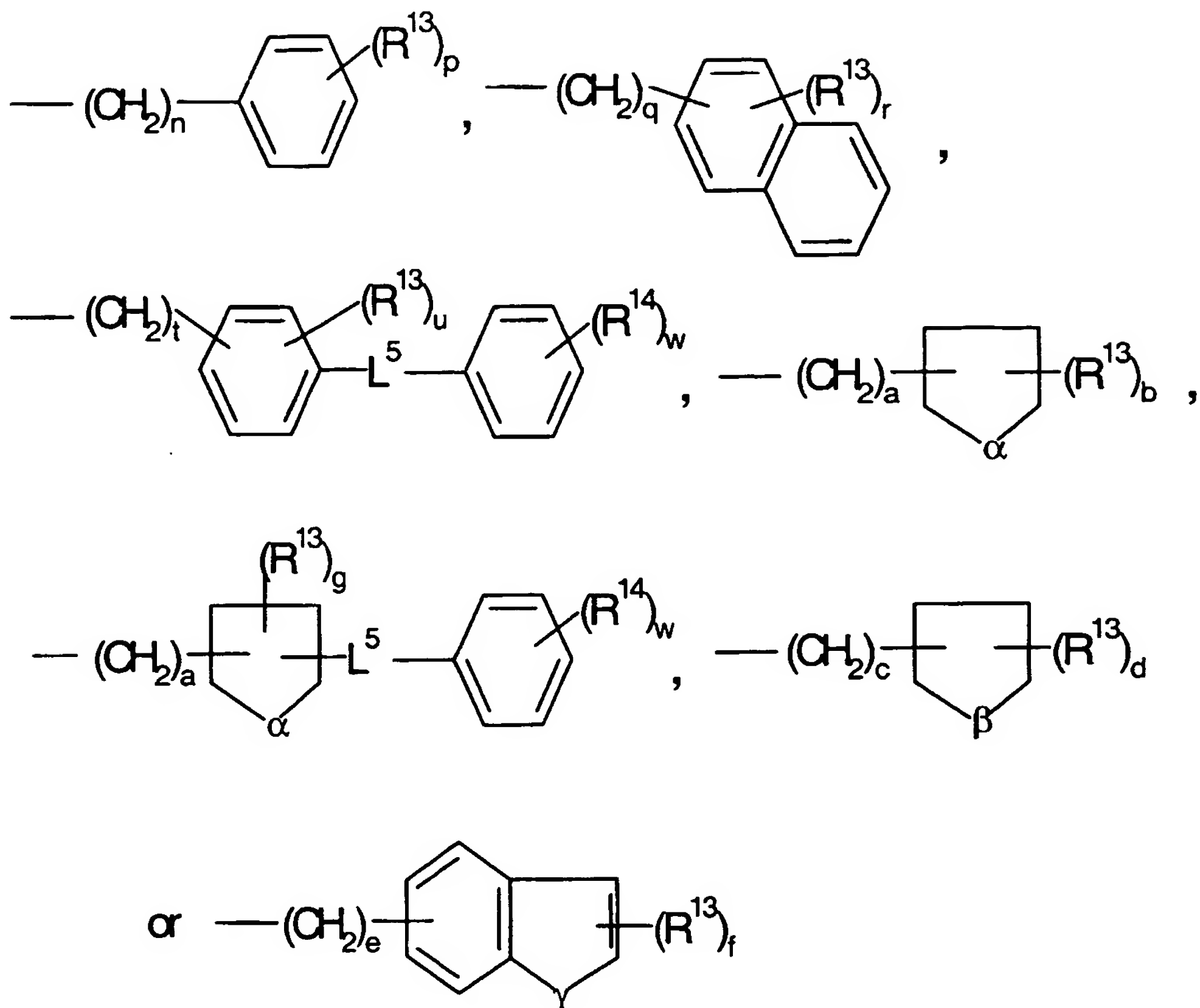
Particularly preferred are compounds wherein for R₁
 5 the combined group -(L₁)-R₁₁ is selected from the group
 consisting of



where R₁₂ is a radical independently selected from halo,
 C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), -O-(C₁-C₈
 10 alkyl) and C₁-C₈ haloalkyl where t is a number from 0 to
 5 and u is a number from 0 to 4 is the group -(L₁)-R₁₁;
 where, -(L₁)- is a divalent linking group of 1 to 8
 atoms and where R₁₁ is a group selected from (a) or (b).

15 Preferred for R₁₁ is -(CH₂)_m-R¹² wherein m is an
 integer from 1 to 6, and R¹² is (d) a group represented by
 the formula:

-22-



wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8

5 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$,

$-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur

10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer

-23-

from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen.

5

Preferred R₂ substituents:

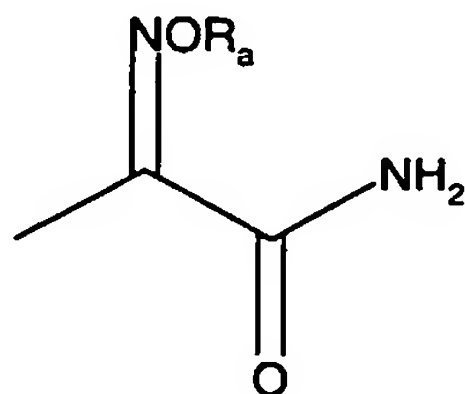
R₂ is preferably selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, -O-(C₁-C₃ alkyl),

10 -S-(C₁-C₃ alkyl), -C₃-C₄ cycloalkyl -CF₃, halo, -NO₂, -CN, -SO₃. Particularly preferred R₂ groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃.

15 **Preferred R₃ substituents:**

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

Another preferred subclass of compounds of
20 formula (I) are those wherein Z is an oxime amide group.



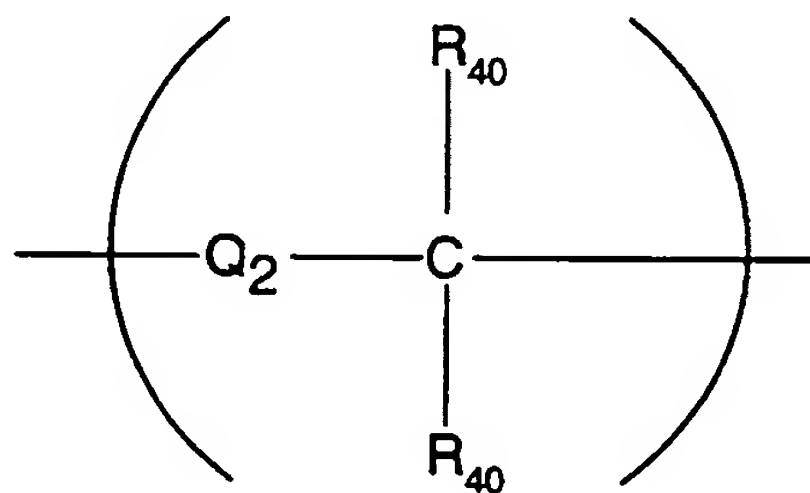
-24-

Also preferred are compounds of formula (I) wherein R_3 is an oxime amide group and R_a is hydrogen, methyl or ethyl. For the group R_3 it is preferred that the linking group $-(L_3)-$ be a bond.

5

Preferred R_4 substituents:

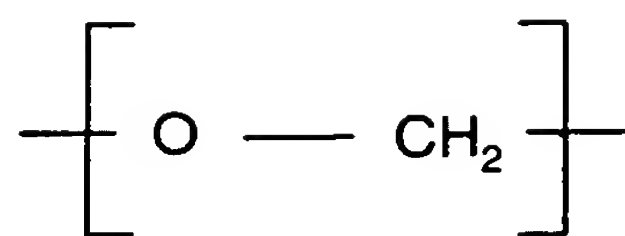
Another preferred subclass of compounds of formula (I) are those wherein R_4 is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, $-(L_C)-$, for R_4 is selected from a group represented by the formula;



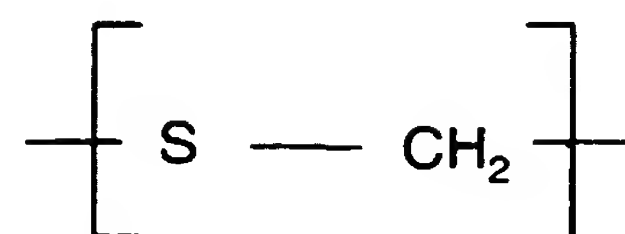
where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$, $-C(O)-$, and $-S-$, and each R_{40} is independently selected from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8 alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, $-(L_C)-$, for R_4 is selected from the specific groups;

20

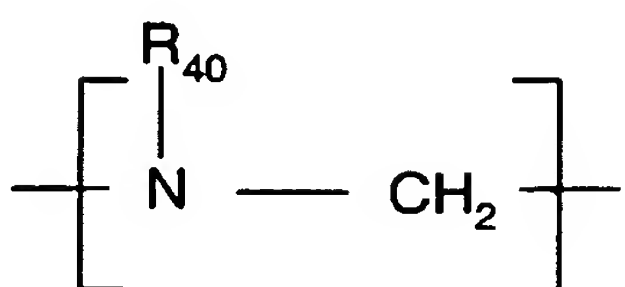
-25-



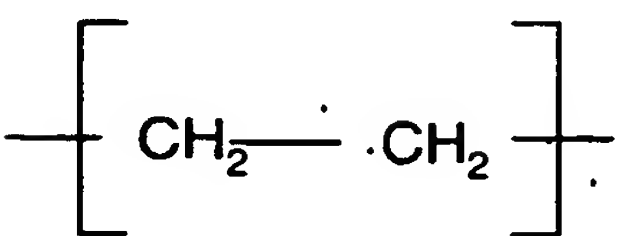
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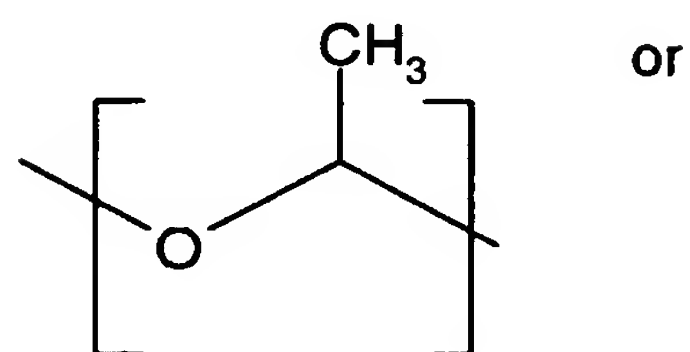
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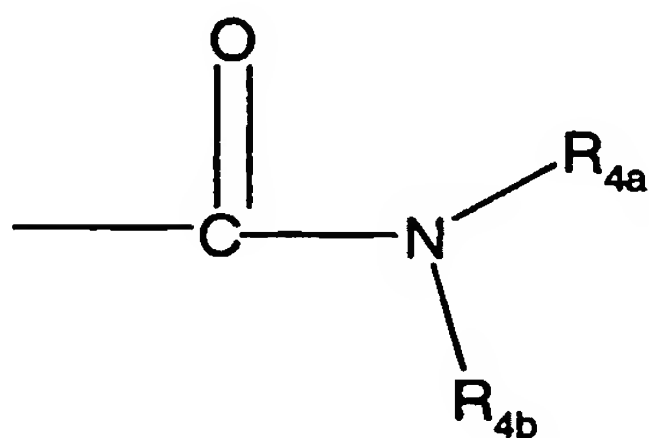


,

where R_{40} is hydrogen or C_1 - C_8 alkyl.

Preferred as the (acylamino acid group) in the group R_4

5 is the group:



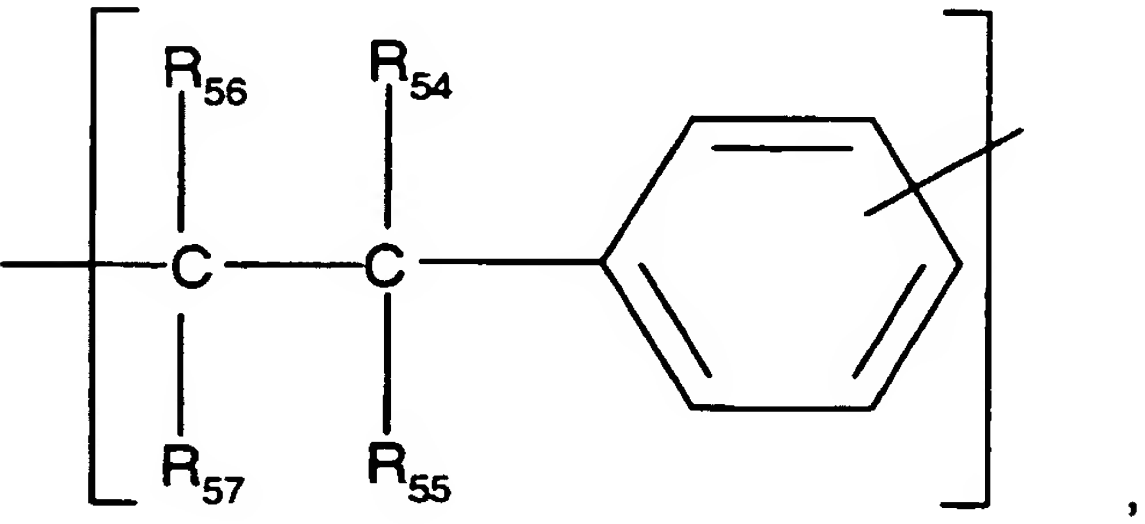
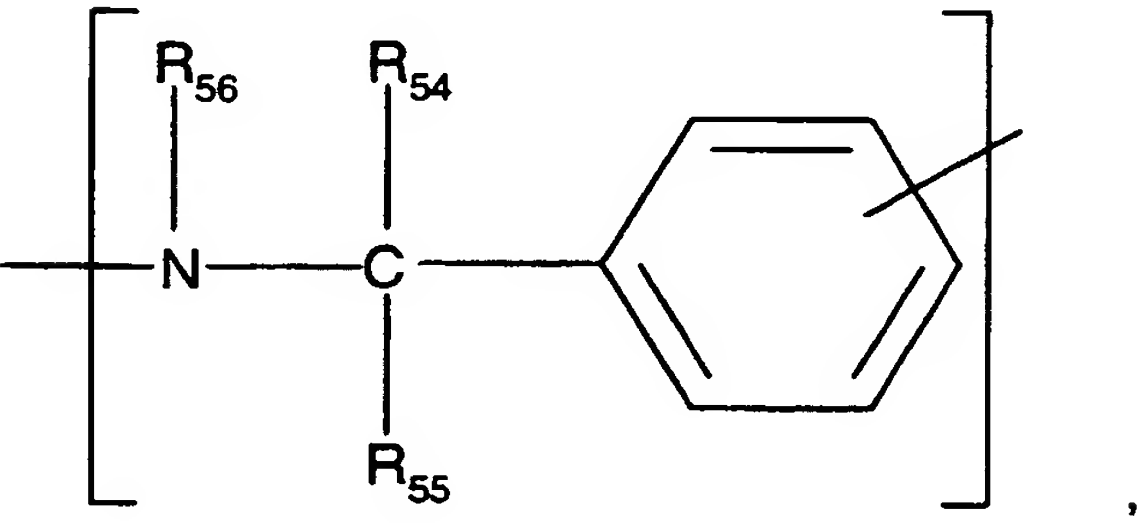
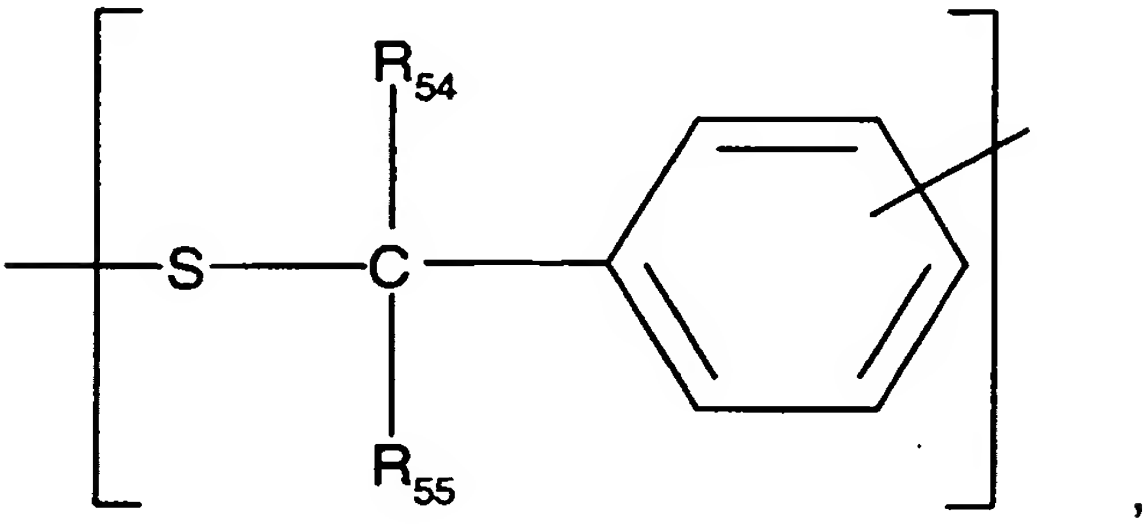
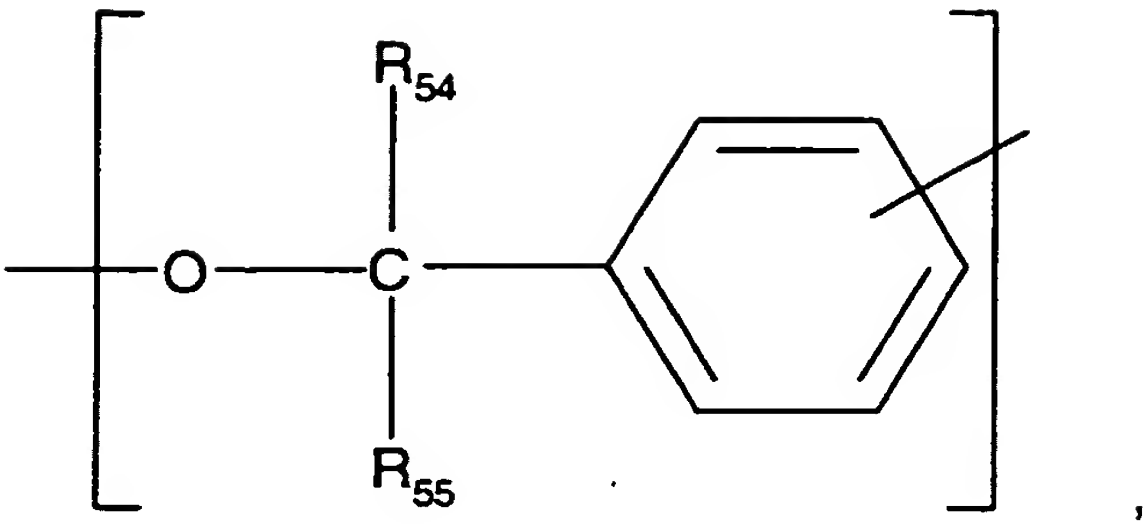
-26-

wherein R^{4a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof. A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

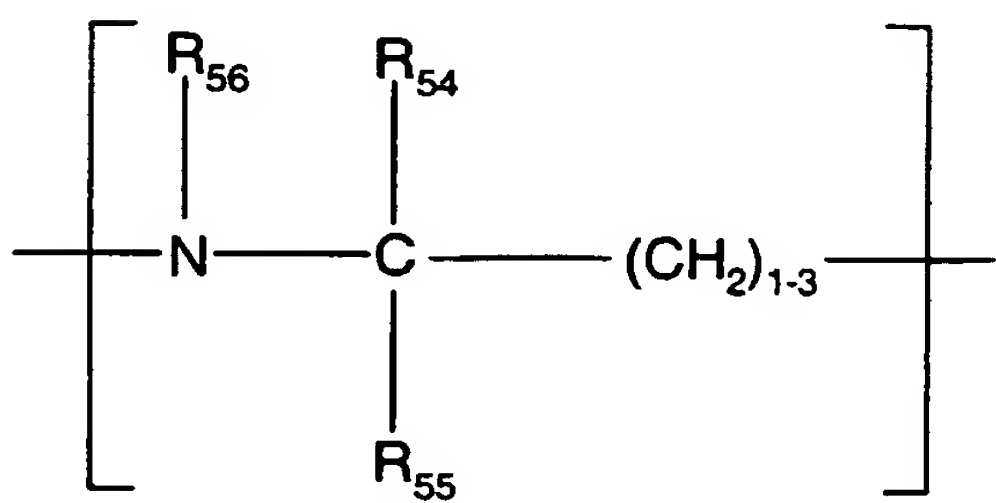
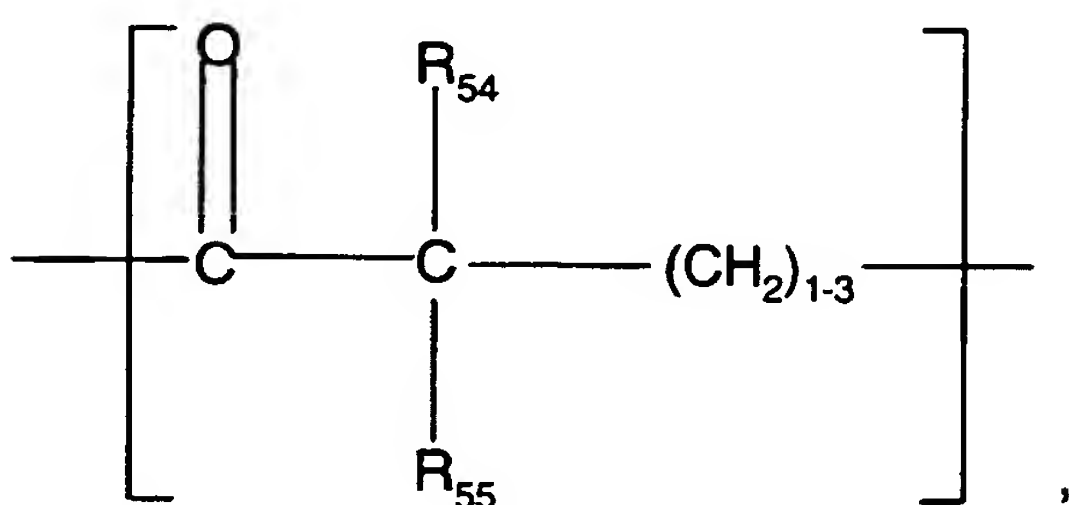
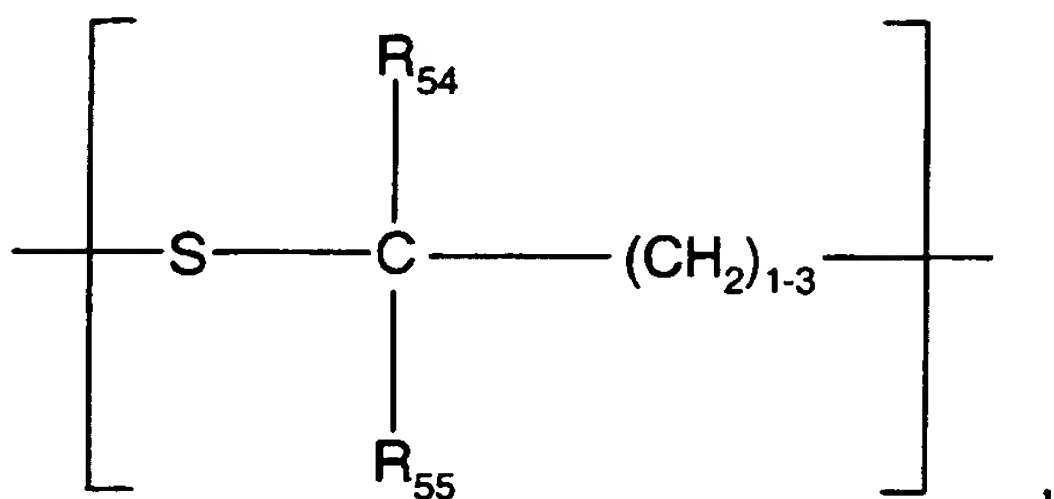
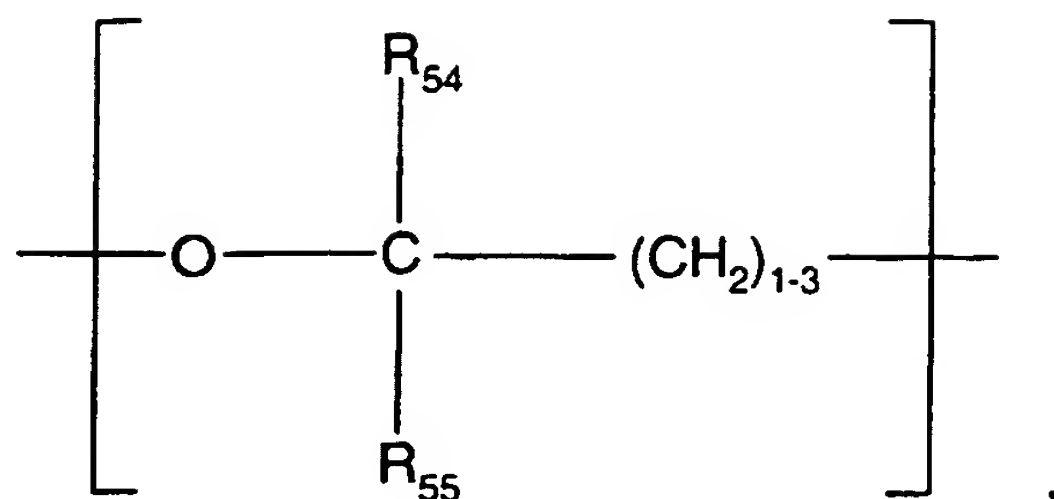
Particularly preferred are R^{4b} groups that combine with the nitrogen atom to represent amino acid residues from the amino acid groups selected from: glycine, glycine methyl ester, L-alanine, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenylalanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L-valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

Preferred R₅ Substituents:

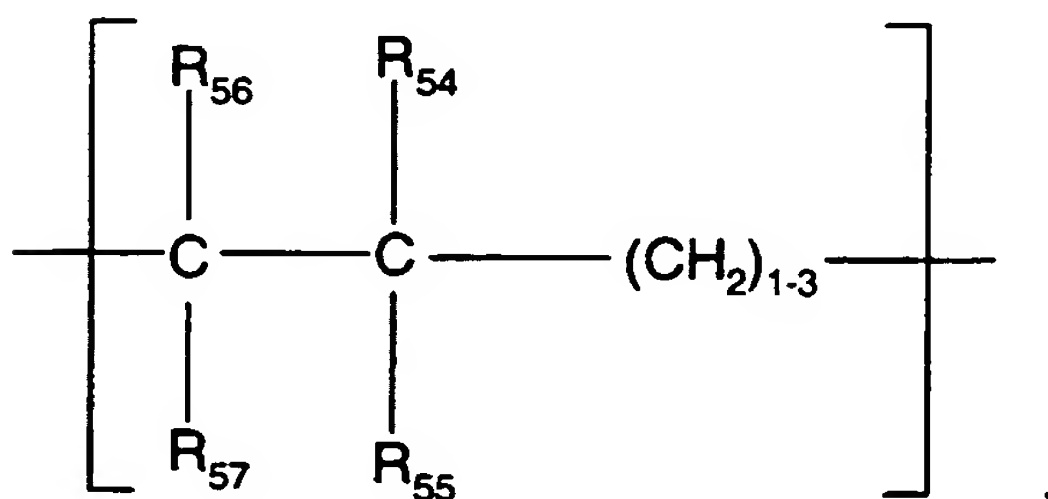
Preferred acid linker, -(L_a)-, for R₅ is selected from the group consisting of;



-28-



and



-29-

wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo. Preferred (acidic group) for R₅ is selected from the group consisting of -CO₂H, -SO₃H and

5 -P(O)(OH)₂.

Preferred R₆ and R₇ substituents:

Another preferred subclass of compounds of formula (I) are those wherein for R₆ and R₇ the non-

10 interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆

15 alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆

20 alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆ haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H,

25 chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,

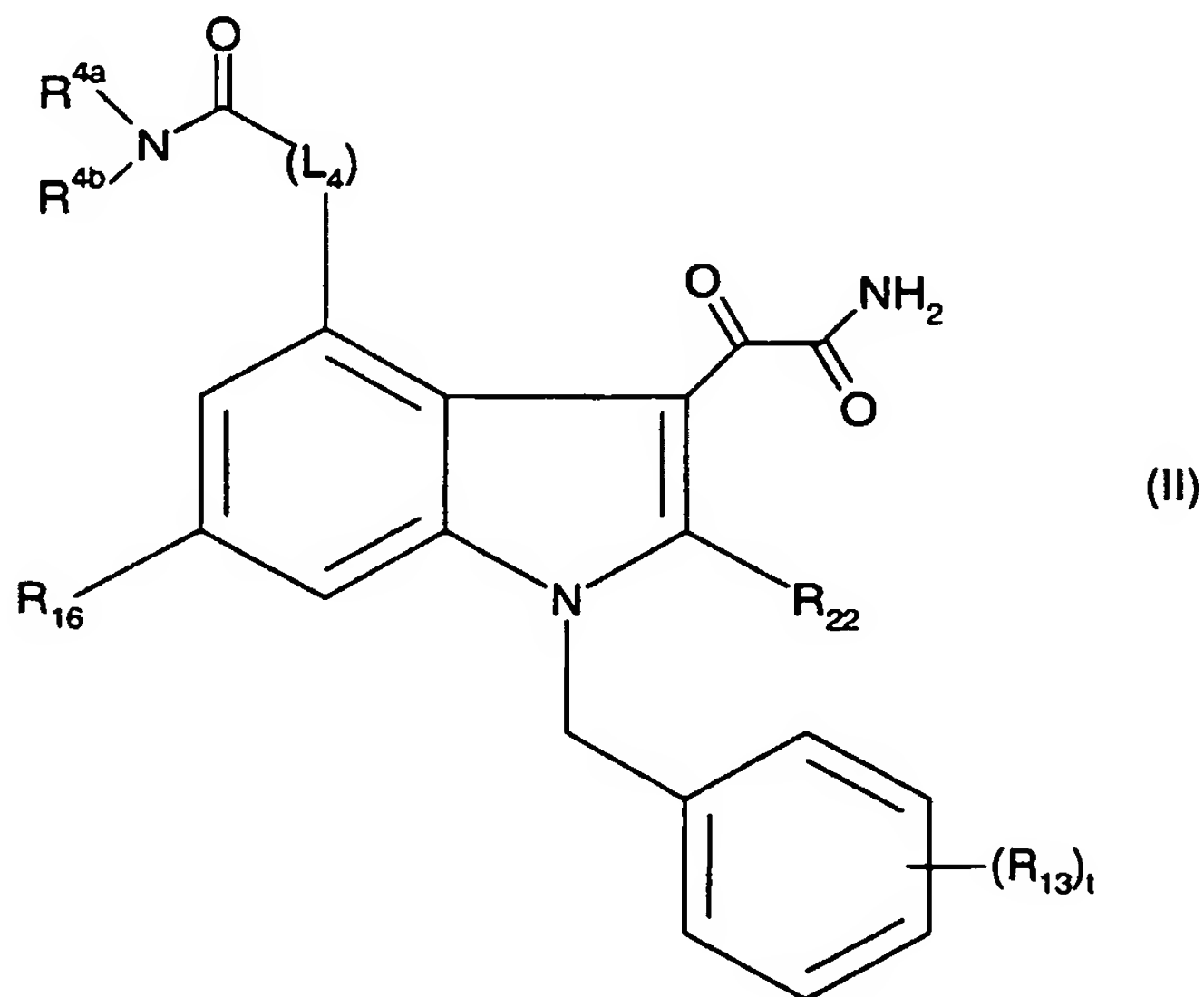
-30-

iodo, nitro, phosphono, $-\text{SO}_3\text{H}$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

Most preferred as non-interfering substituents are
5 methyl, ethyl, propyl, and isopropyl.

Preferred compounds of the invention are those having the general formula (II), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;

10

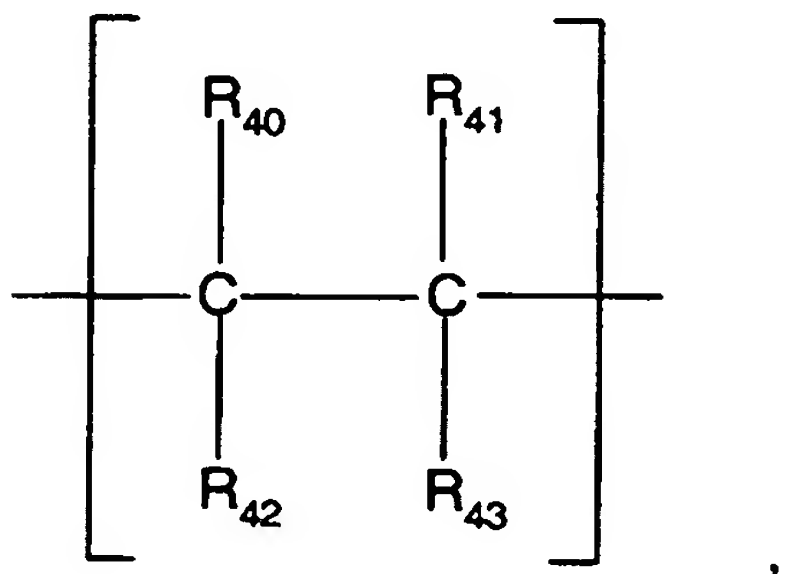
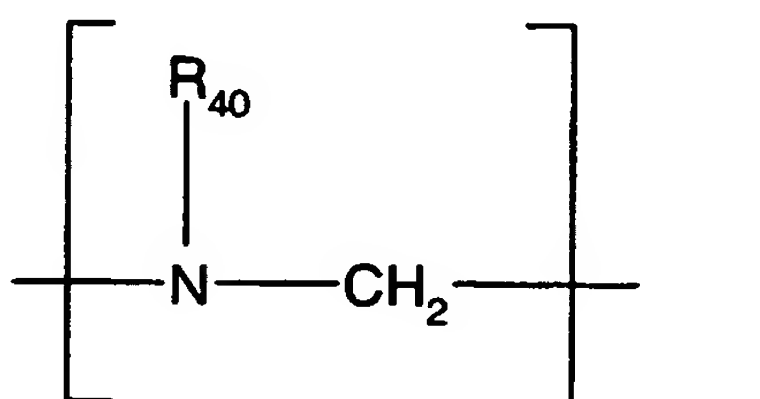
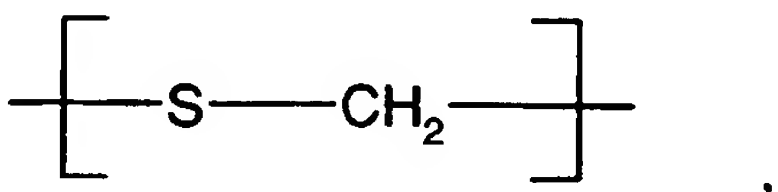
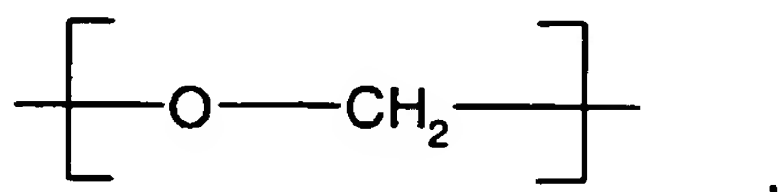


wherein ;

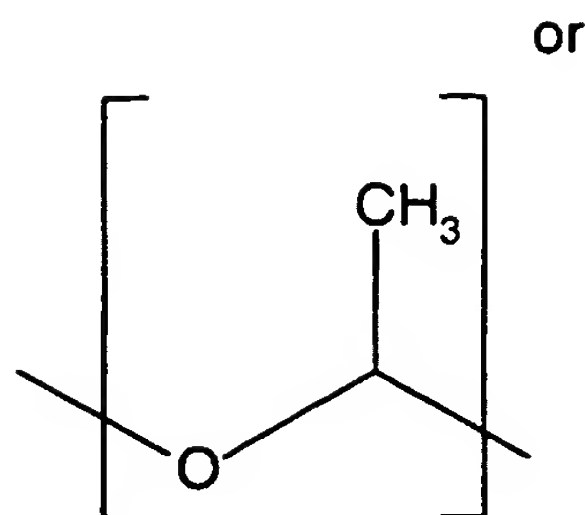
15 R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-\text{F}$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, or $-\text{O}-\text{CH}_3$;

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wherein R^{4a} is selected from the group consisting of H,
 (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and
 wherein NR^{4b} is an amino acid residue of either a
 natural or unnatural amino acid with the nitrogen atom
 5 being part of the amino group of the amino acid. A
 preferred R^{4a} group is the group hydrogen (H); and -
 (L₄)- is a divalent group selected from;



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where R_{40} , R_{41} , R_{42} , and R_{43} are each independently selected from hydrogen or C₁-C₈ alkyl.

R_{16} is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, and halo.

R_{13} is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈, phenyl, halophenyl, hydroxyalkyl, and halo, and t is an integer from 0 to 5.

Preferred specific compounds (and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof) which are illustrative of the compounds of the invention are as follow:

N -[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

N -[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]glycine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

5 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

10 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

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The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups
5 various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium,
10 magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

15 Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous
20 bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable
25 organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,

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bitartrate, borate, bromide, camsylate, carbonate,
chloride, clavulanate, citrate, chloride, edetate,
edisylate, estolate, esylate, fluoride, fumarate,
gluceptate, gluconate, glutamate, glycolylarsanilate,
5 hexylresorcinate, bromide, chloride, hydroxynaphthoate,
iodide, isothionate, lactate, lactobionate, laurate,
malate, malseate, mandelate, mesylate, methylbromide,
methylnitrate, methylsulfate, mucate, napsylate, nitrate,
oleate, oxalate, palmitate, pantothenate, phosphate,
10 polygalacturonate, salicylate, stearate, subacetate,
succinate, tannate, tartrate, tosylate, trifluoroacetate,
trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or
15 more chiral centers and may thus exist in optically active
forms. Likewise, when the compounds contain an alkenyl or
alkenylene group there exists the possibility of cis- and
trans- isomeric forms of the compounds. The R- and S-
isomers and mixtures thereof, including racemic mixtures
20 as well as mixtures of cis- and trans- isomers, are
contemplated by this invention. Additional asymmetric
carbon atoms can be present in a substituent group such as
an alkyl group. All such isomers as well as the mixtures
thereof are intended to be included in the invention. If
25 a particular stereoisomer is desired, it can be prepared
by methods well known in the art by using stereospecific

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reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

5 For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can

10 be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable

15 groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative

20 form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid

25 derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides

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prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

10

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

15

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

20

a) The 1H-indole-3-glyoxylamide amino derivative compounds of the invention are prepared by room temperature base catalyzed condensation of the amino acid protected at the acid terminus by protecting group

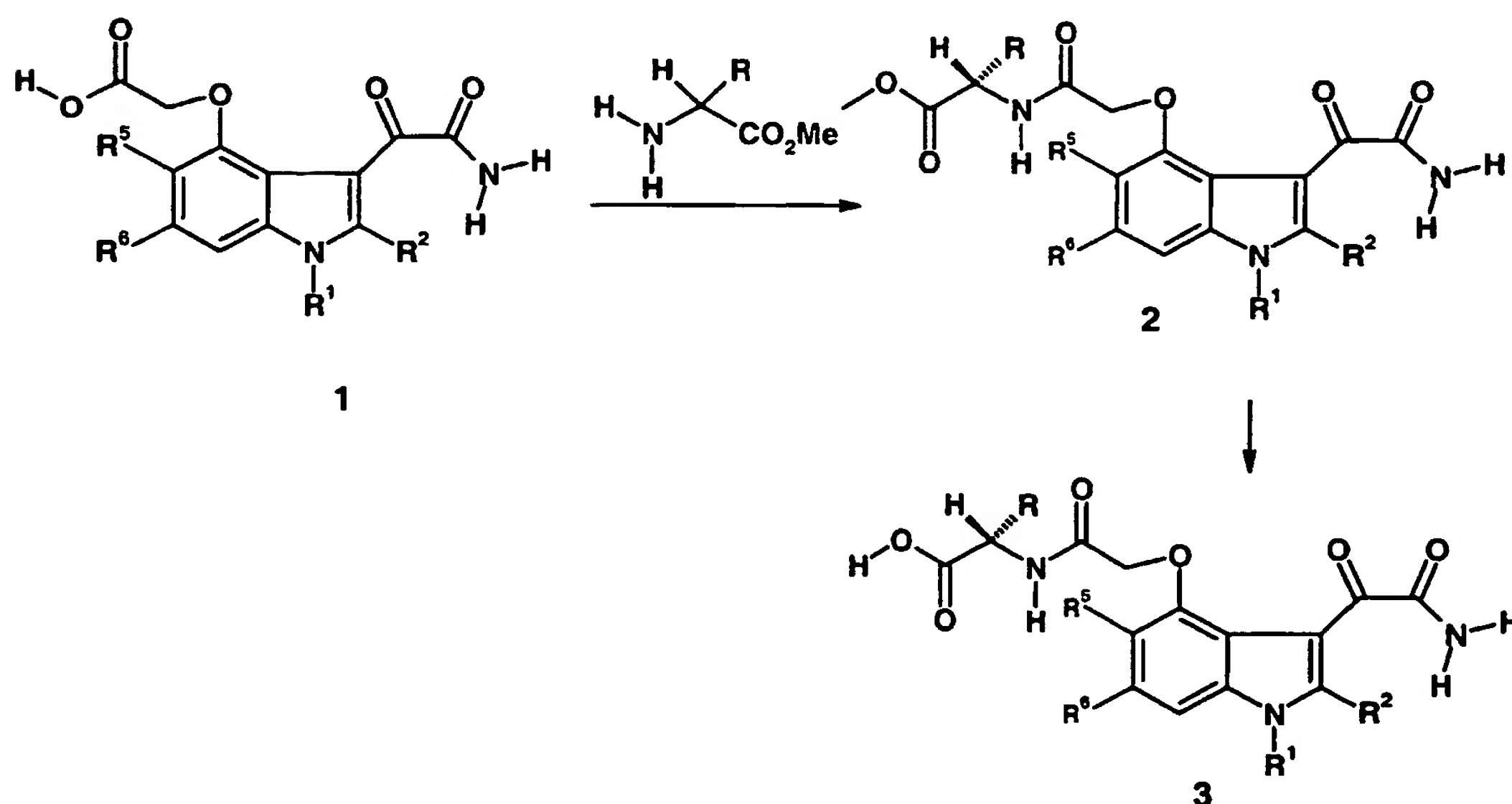
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known in the literature but preferably as the methyl ester with the 1H-indole-3-glyoxylamide acid derivative compound of formula (1) as shown in Scheme I:

5

Scheme 1



Typically, the condensation or coupling is performed in a solvent such as dimethyl formamide, tetrahydrofuran or aqueous mixtures of the like. In general protic solvents are preferred for the purpose of this invention. The reaction is catalyzed by a base including weak organic or inorganic bases. Organic bases such as collidine are preferred. The reaction is also preferably run in the presence of agents that retard or reduce racemization of the amino acid or its

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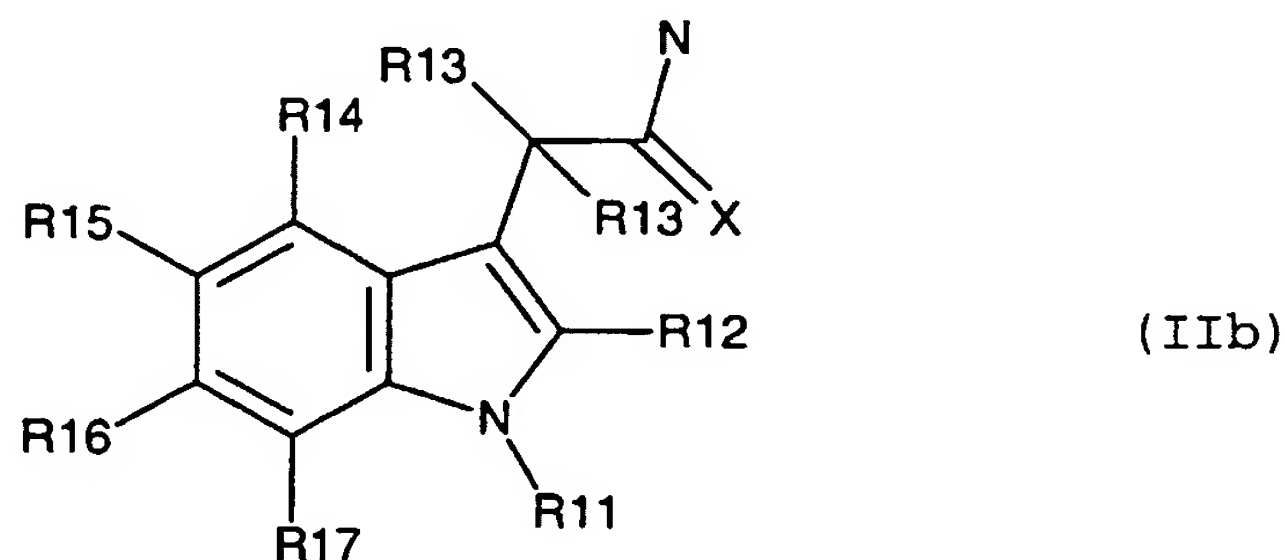
derivative, such as for example, benzotriazolyl-N-oxy-
tris(dimethylamino)phosphonium hexafluorophosphate.
Upon completion of the reaction, the mixture is
concentrated in vacuo. The resulting product mixture is
5 chromatographed to obtain the target compound.

One of skill in the art is aware that the derivatives
of the acid such as the acid salt or the methyl ester of
the acid, can be reacted with the amino acid or
10 derivatives thereof to obtain the protected compound 2 or
a corresponding derivative. Such methods are well known
in the arts and can be found in reference texts such as
for example J. March Advanced Organic Chemistry, Wiley
Interscience publishers, New York, N.Y, 1985, and R. C.
15 Larock Comprehensive Organic Transformations, VCH
Publishers, New York, N.Y, 1989. The protected compounds
of formula (2) are also useful sPLA₂ inhibitors and are
also compounds of this invention.

20 b) 1H-indole-3-acetamide amino acid derivative
sPLA₂ inhibitors are similarly prepared by condensation of
the protected amino acid with the 1H-indole-3-acetamide
sPLA₂ inhibitor. The 1H-indole-3-acetamide sPLA₂
inhibitors and methods of making them are set out in U.S.
25 Patent No. 5,684,034, the entire disclosure of which is
incorporated herein by reference. Indole-3-acetamide

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amino acid derivative sPLA2 inhibitors of this invention are represented by compounds of formula (IIb), and pharmaceutically acceptable salts and prodrug derivatives thereof,



5

wherein ;

X is oxygen or sulfur;

R₁₁ is selected from groups (i), (ii) (iii) and (iv)

10 where;

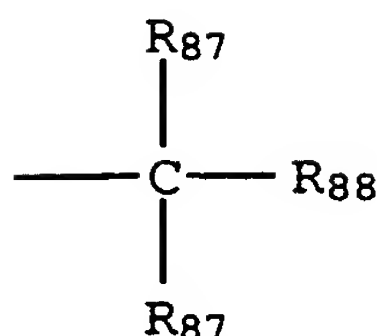
(i) is C₆-C₂₀ alkyl, C₆-C₂₀ alkenyl, C₆-C₂₀ alkynyl, C₆-C₂₀ haloalkyl, C₄-C₁₂ cycloalkyl, or

(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C₁-C₁₀ alkyl, C₁-C₁₀ alkylthio, C₁-C₁₀ alkoxy, carboxyl, amino, or hydroxyamino; or

15 (iii) is -(CH₂)_n-(R₈₀), or -(NH)-(R₈₁), where n is 1 to 8, and R₈₀ is a group recited in (i), and R₈₁ is selected from a group recited in (i) or (ii);

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(iv) is



where R₈₇ is hydrogen or C₁-C₁₀ alkyl, and R₈₈ is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C₁-C₁₀ alkylthio, C₁-C₁₀ alkoxy, phenyl, nitro, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

R₁₂ is halo, C₁-C₂ alkylthio, C₁-C₂ alkyl, C₁-C₂ alkyaryl or C₁-C₂ alkoxy;

each R₁₃ is independently hydrogen, halo, or methyl;

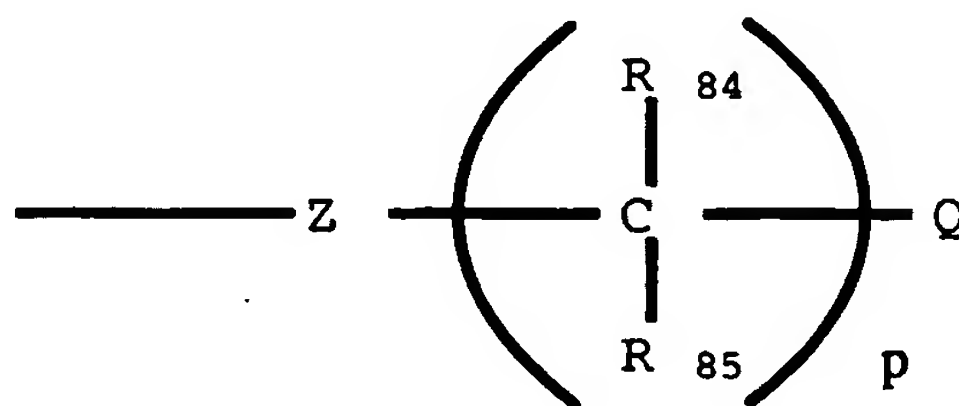
R¹⁴ is the group -L_C-[acylamino acid], wherein the acylamino acid group is -C(O)-NR^{14a}R^{14b} wherein R^{14a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl; and -L_C- is as defined *supra*, and wherein NR^{14b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. Most preferred are compounds of formula II wherein the group R^{14a} is a hydrogen atom (H). A preferred source of the amino acid residue NR^{14b} is an amino acid selected from the group comprising isoleucine, valine, phenylalanine,

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aspartic acid, leucine, glycine and isomers and derivatives thereof;

R₁₅ is selected from hydrogen, a non-interfering substituent, or the group, -(L_a)-(acidic group); wherein
 5 -(L_a)-, is an acid linker having an acid linker length of 1 to 8;

R₁₆ and R₁₇ are each independently hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₈ cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in
 10 the set R₁₅, R₁₆, and R₁₇, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C₁-C₁₀ haloalkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ haloalkoxy, C₄-C₈ cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN,
 15 C₁-C₁₀ alkylthio, arylthio, thioacetal, -C(O)O(C₁-C₁₀ alkyl), hydrazide, hydrazino, hydrazido, -NH₂, -NO₂, -NR₈₂R₈₃, and -C(O)NR₈₂R₈₃, where, R₈₂ and R₈₃ are independently hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ hydroxyalkyl, or taken together with N, R₈₂ and R₈₃ form a 5- to 8-
 20 membered heterocyclic ring; or a group having the formula;



where,

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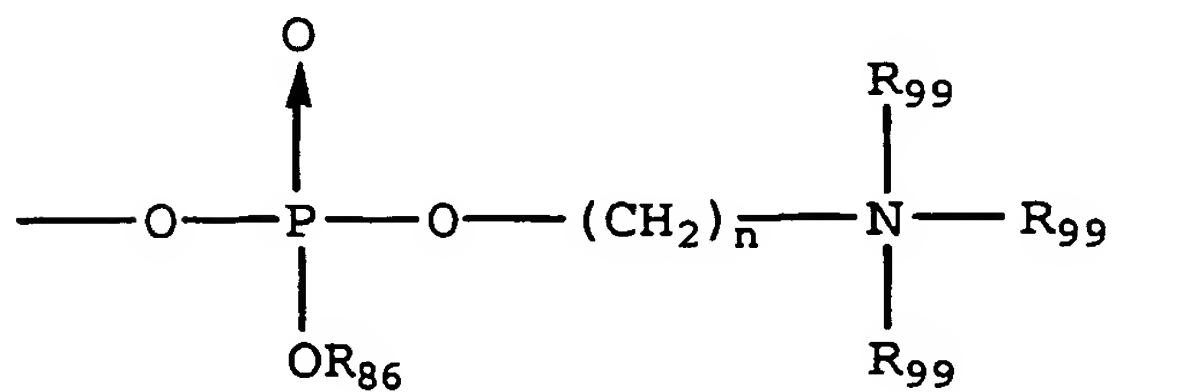
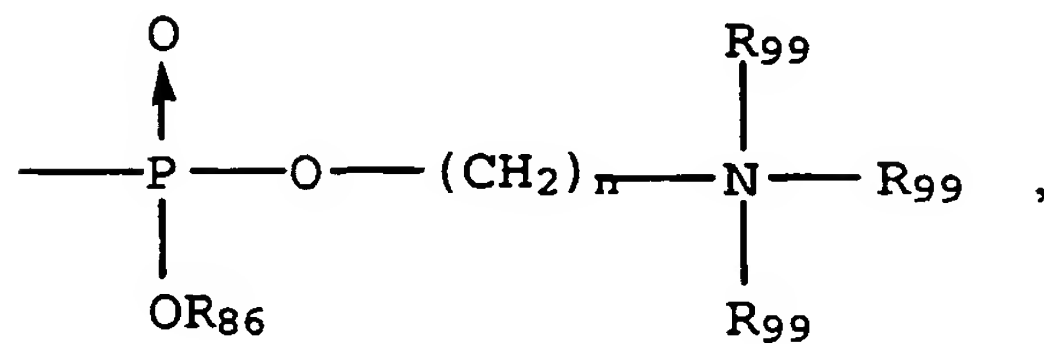
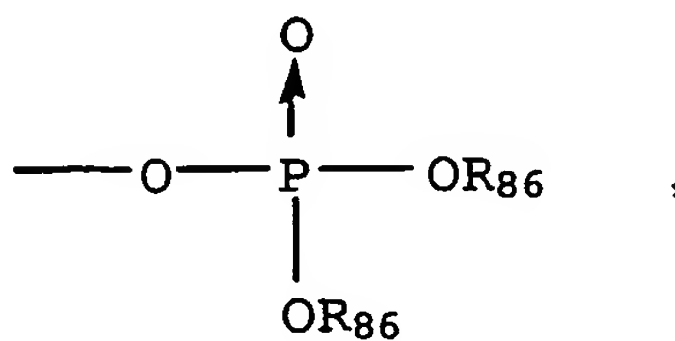
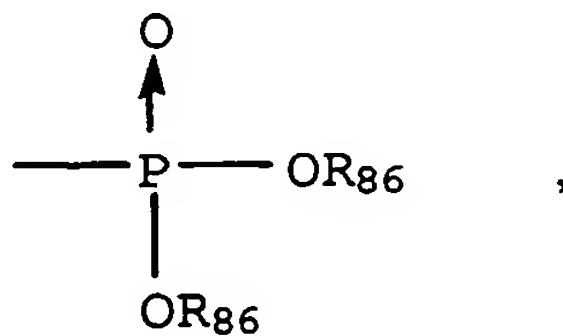
R₈₄ and R₈₅ are each independently selected from hydrogen, C₁-C₁₀ alkyl, hydroxy, or R₈₄ and R₈₅ taken together are =O;

p is 1 to 5,

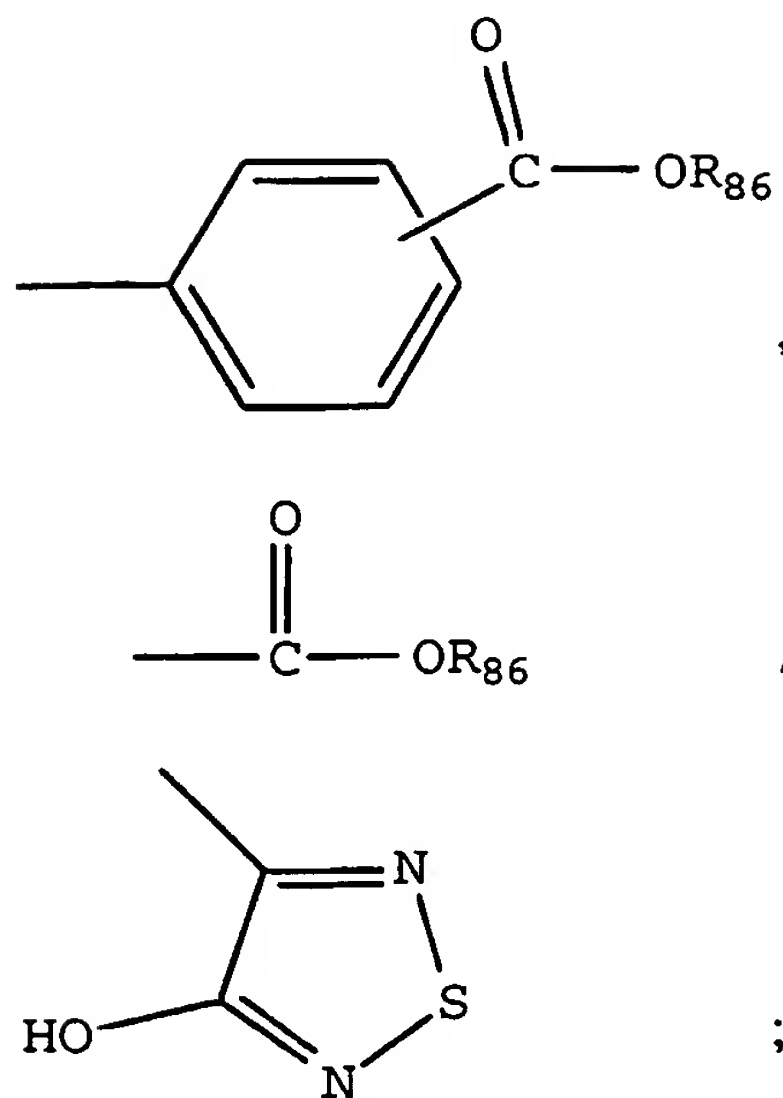
5 Z is a bond, -O-, -N(C₁-C₁₀ alkyl)-, -NH-, or -S-;

and

Q is -CON(R₈₂R₈₃), -5-tetrazolyl, -SO₃H,

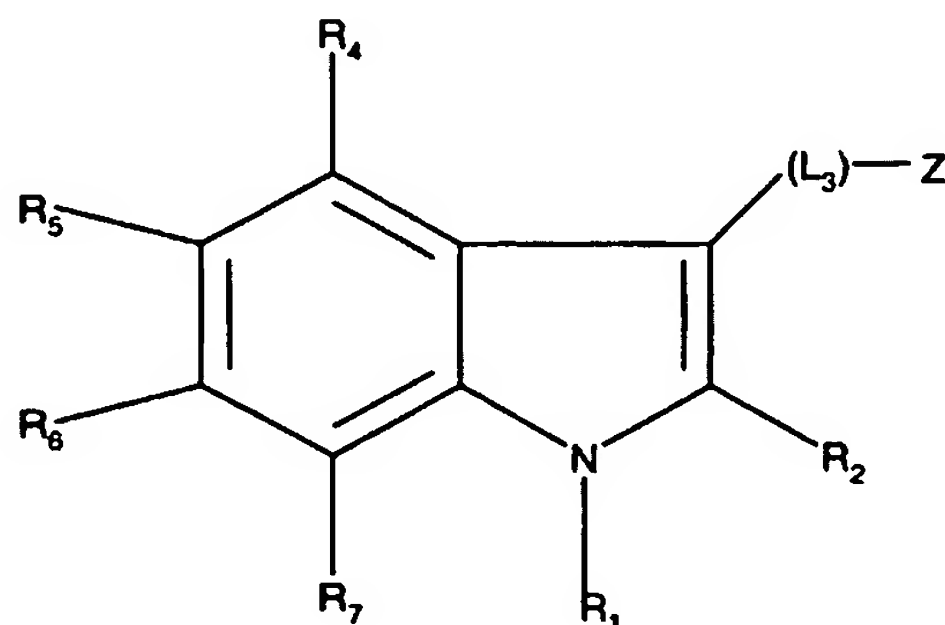


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where n is 1 to 8, R_{86} is independently selected from hydrogen, a metal, or C_1 - C_{10} alkyl, and R_{99} is selected
 5 from hydrogen or C_1 - C_{10} alkyl.

c) Indole-3-Oxime amide compounds of the invention are represented by compounds of formula (III) or a pharmaceutically acceptable salt, solvate or prodrug
 10 thereof;



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wherein ;

R_1 is selected from groups (a), (b), and (c)

wherein;

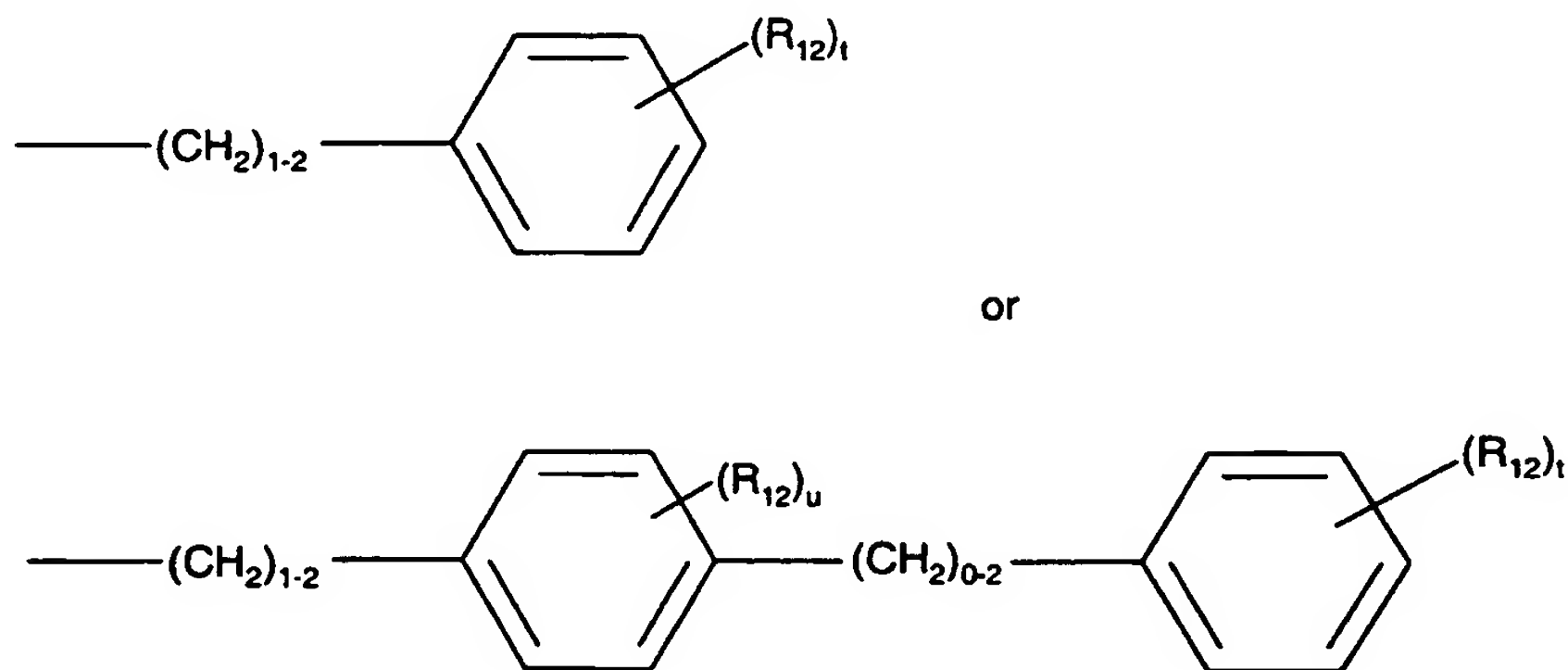
5 (a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or more independently selected non-interfering

10 substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b).

15 Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of

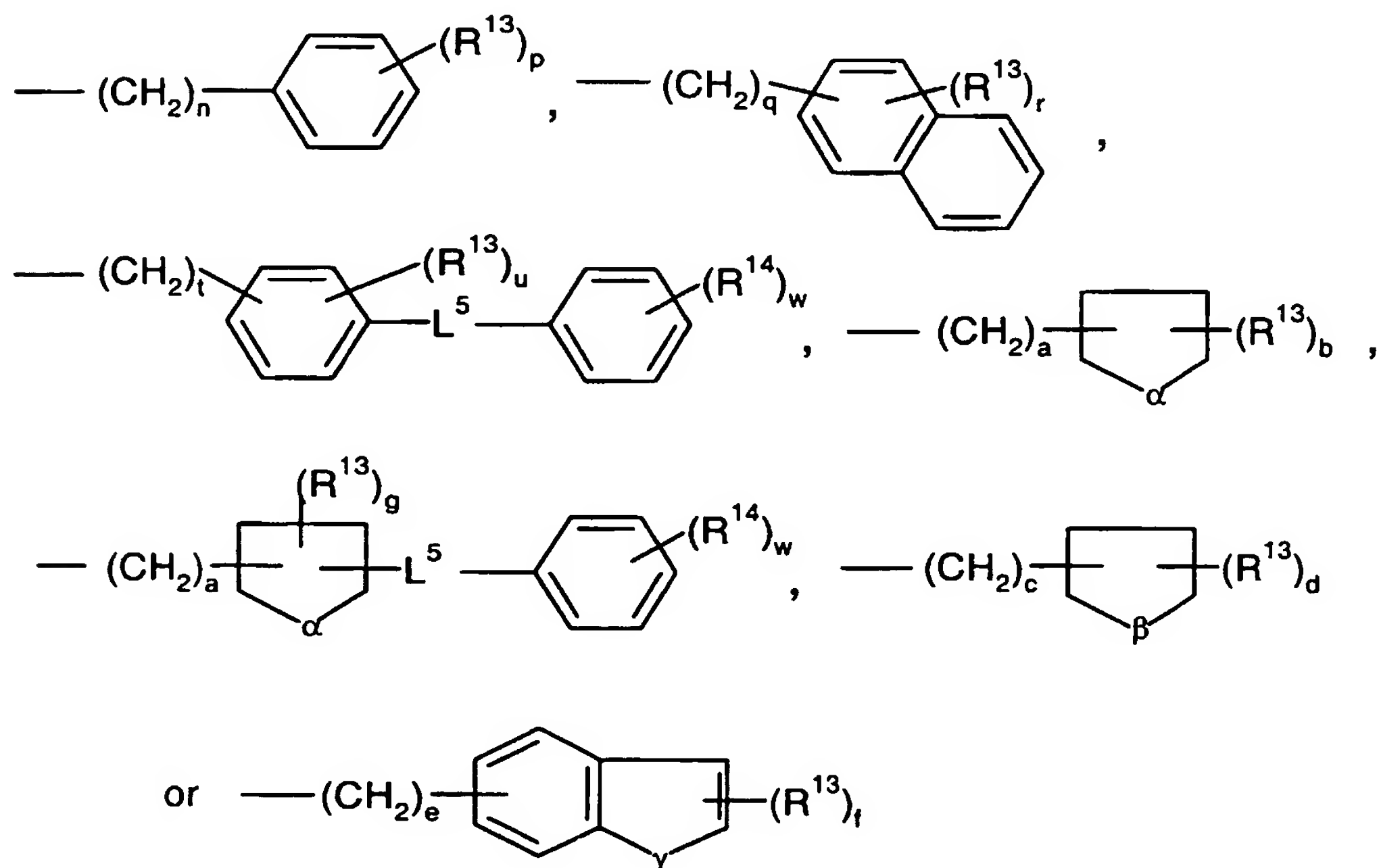


-47-

where R_{12} is a radical independently selected from halo, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8 \text{ alkyl})$ and C_1 - C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

5

Also preferred for R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by the formula:



10

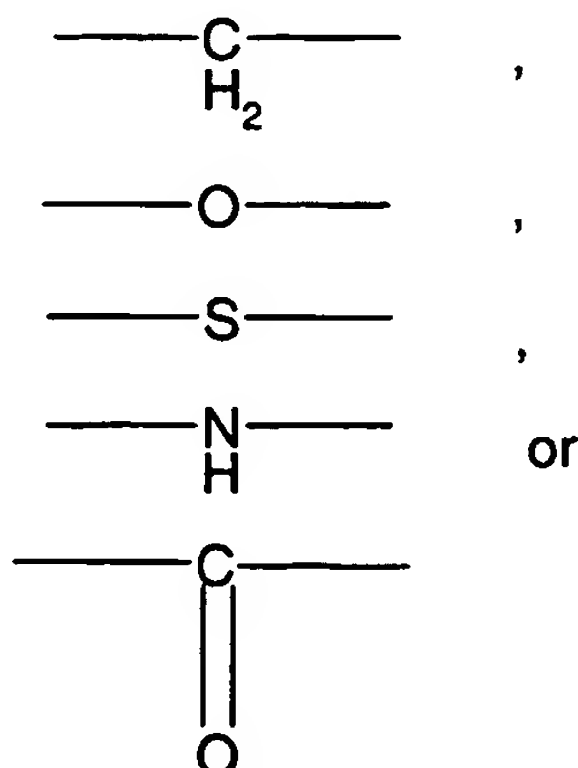
wherein a , c , e , n , q , and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to

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C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5
 is a bond, $-(CH_2)_v-$,
 $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β
 is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur
 5 atom, b is an integer from 0 to 3, d is an integer from
 0 to 4, f , p , and w are independently an integer from 0
 to 5, r is an integer from 0 to 7, and u is an integer
 from 0 to 4, or is (e) a member of (d) substituted with
 at least one substituent selected from the group
 10 consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8
 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

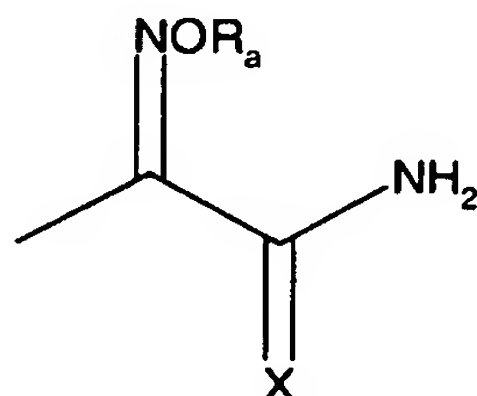
R_2 is hydrogen, or a group containing 1 to 4 non-
 hydrogen atoms plus any required hydrogen atoms;

15 $-(L_3)-Z$, is the group where $-(L_3)-$ is a divalent
 linker group selected from a bond or a divalent group
 selected from:



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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



5

wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R_4 is the group, $-(L_c)-(acylamino\ acid\ group)$; wherein $-(L_c)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

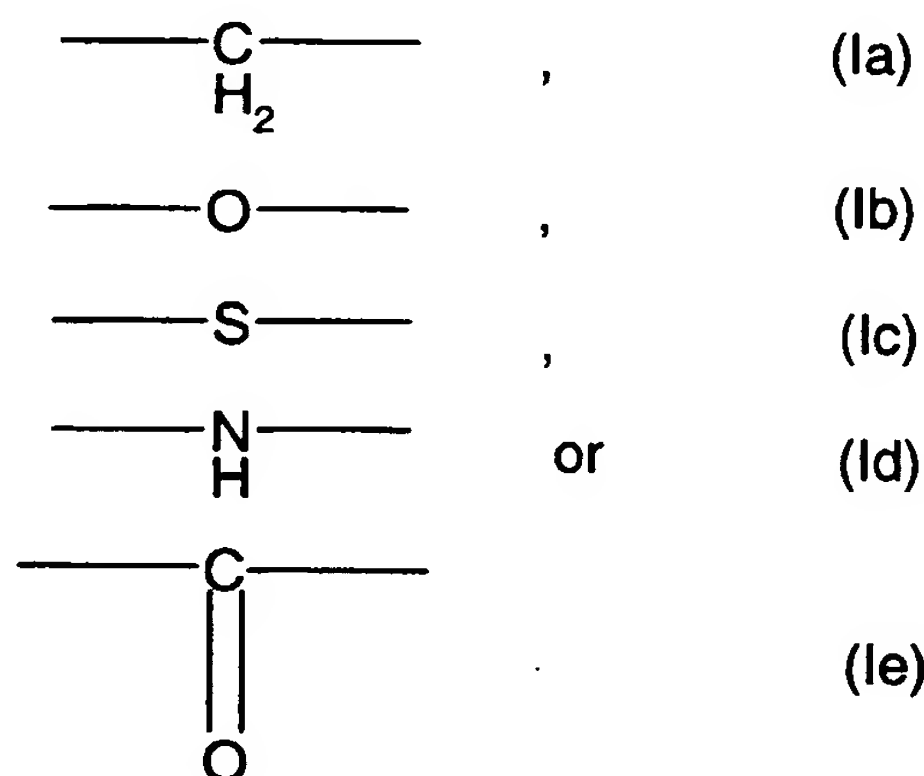
R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein
15 $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8.

R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical,
20 carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

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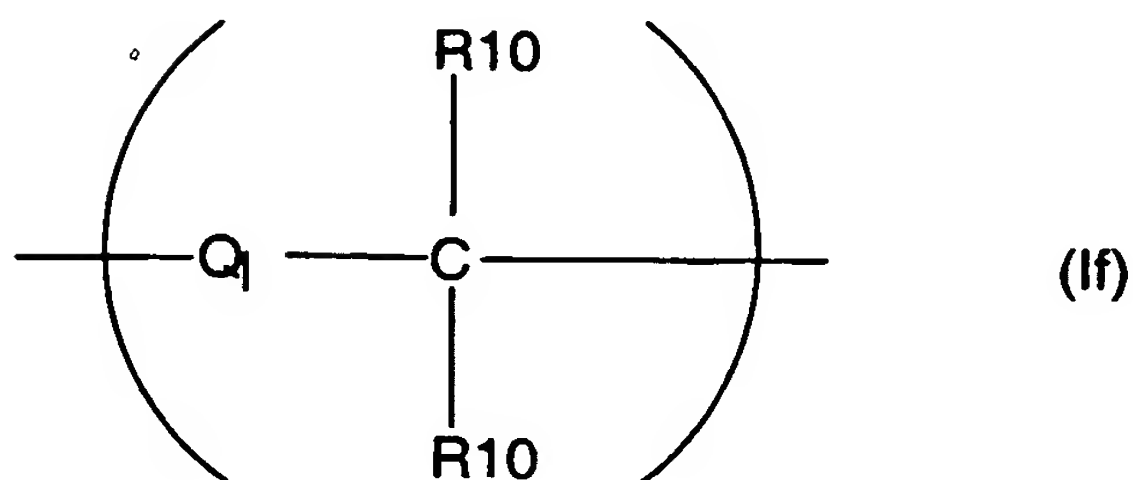
Preferred Subgroups of Compounds of Formula (III):
Preferred R₁ substituents:

A preferred subclass of compounds of formula (III)
 5 are those where for R₁ the divalent linking group -(L₁)-
 is a group represented by any one of the following
 formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



10

or



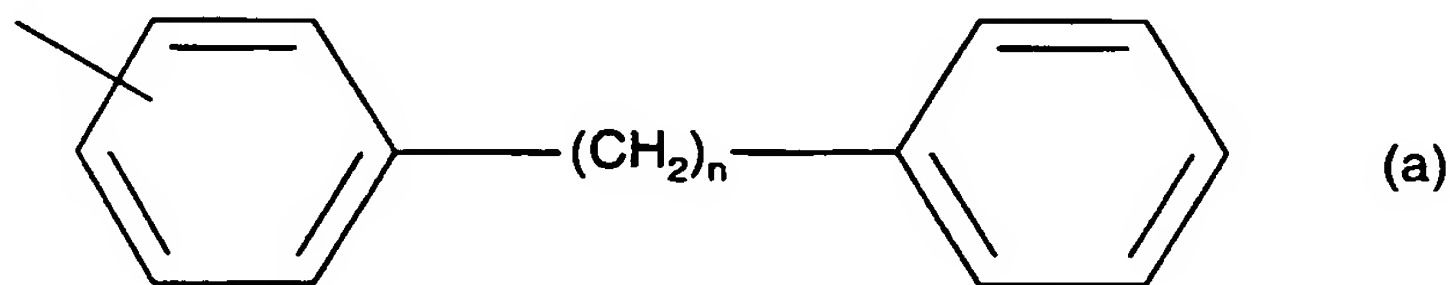
15 where Q₁ is a bond or any of the divalent groups (Ia),
 (Ib), (Ic), (Id), (Ie), and (If) and each R₁₀ is

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independently hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl or C₁₋₈ alkoxy.

Particularly preferred as the linking group -(L₁)- of
5 R₁ is an alkylene chain of 1 or 2 carbon atoms, namely,
-(CH₂)- or -(CH₂-CH₂)-.

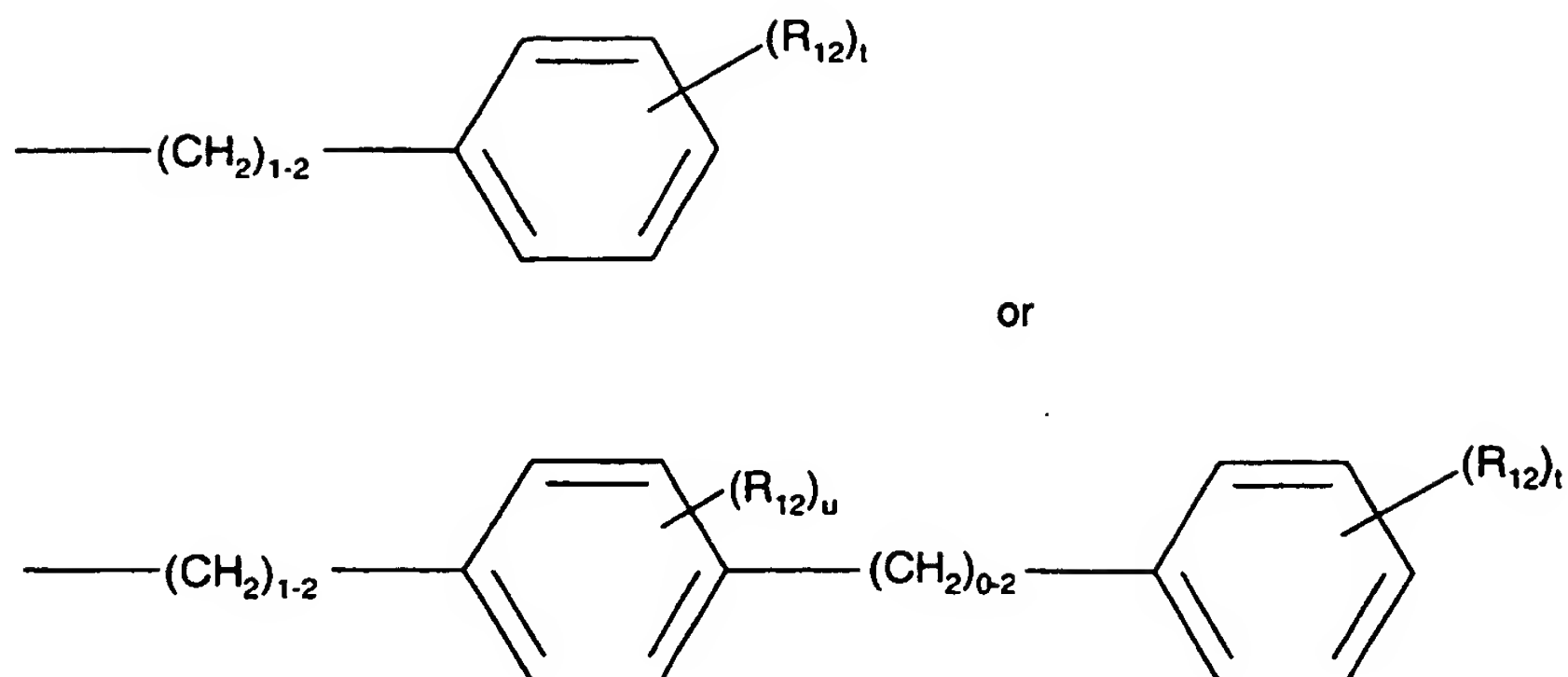
The preferred group for R₁₁ is a substituted or
unsubstituted group selected from the group consisting of
10 C₅-C₁₄ cycloalkyl, C₅-C₁₄ cycloalkenyl, phenyl, naphthyl,
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
indenyl, stilbenyl, terphenyl, diphenylethylenyl,
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
biphenyl, bibenzylyl and related bibenzylyl homologues
15 represented by the formula (a);



where n is a number from 1 to 8.

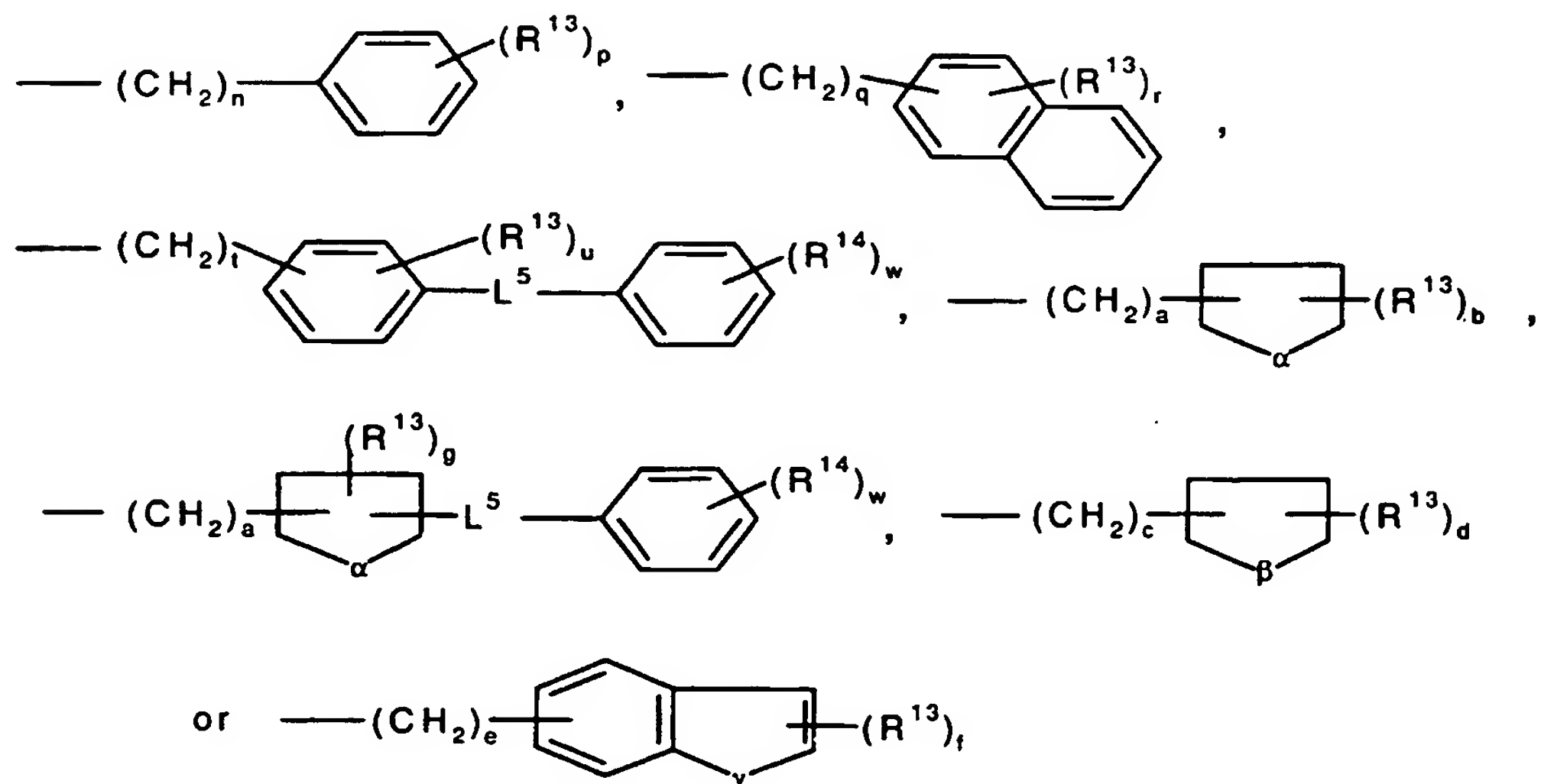
20 Particularly preferred are compounds wherein for R₁
the combined group -(L₁)-R₁₁ is selected from the group
consisting of

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where R₁₂ is a radical independently selected from halo,
 C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), -O-(C₁-C₈
 5 alkyl) and C₁-C₈ haloalkyl where t is a number from
 0 to 5 and u is a number from 0 to 4.

Also preferred for R₁₁ is -(CH₂)_m-R¹² wherein m is an
 integer from 1 to 6, and R¹² is (d) a group represented by
 10 the formula:



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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$, $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

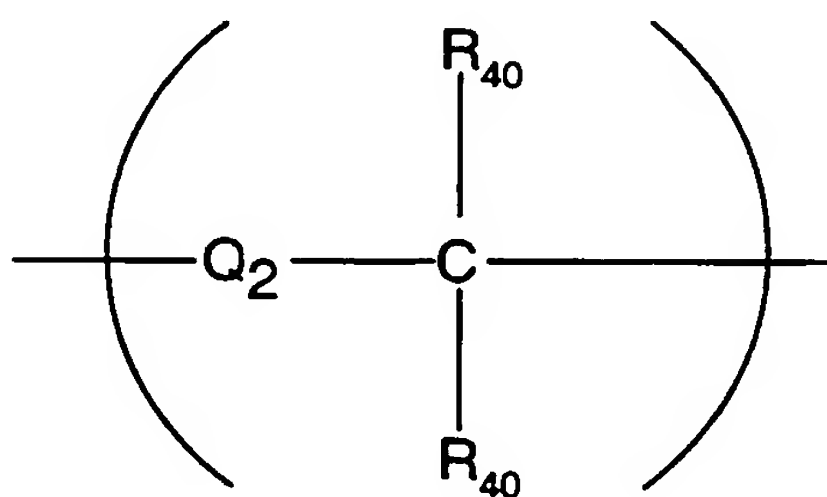
Preferred R_2 substituents:

R_2 is preferably selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, $-O-(C_1-C_3$ alkyl), $-S-(C_1-C_3$ alkyl), $-C_3-C_4$ cycloalkyl $-CF_3$, halo, $-NO_2$, $-CN$, $-SO_3$. Particularly preferred R_2 groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-F$, $-CF_3$, $-Cl$, $-Br$, or $-O-CH_3$.

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Preferred R₄ substituents:

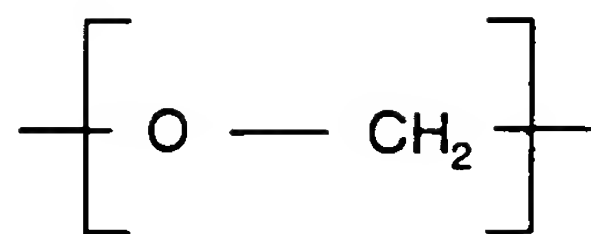
Another preferred subclass of compounds of formula (III) are those wherein R₄ is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, -(L_C)-, for R₄ is selected from a group represented by the formula;



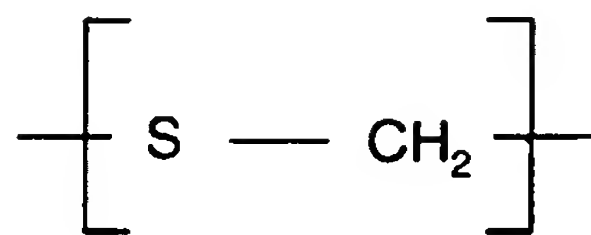
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where Q₂ is selected from the group -(CH₂)-, -O-, -NH-, -C(O)-, and -S-, and each R₄₀ is independently selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, -(L_C)-, for R₄ is selected from the specific groups;

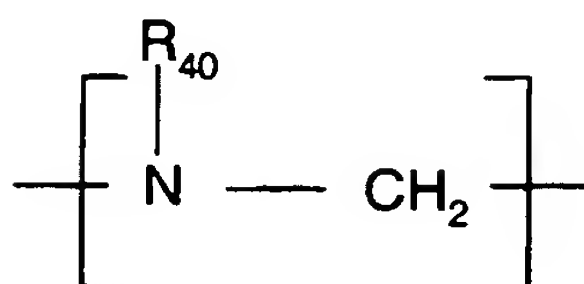
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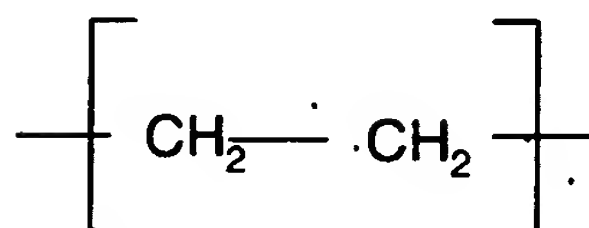
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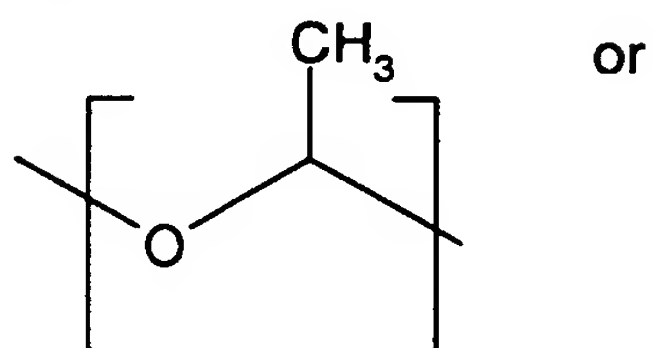
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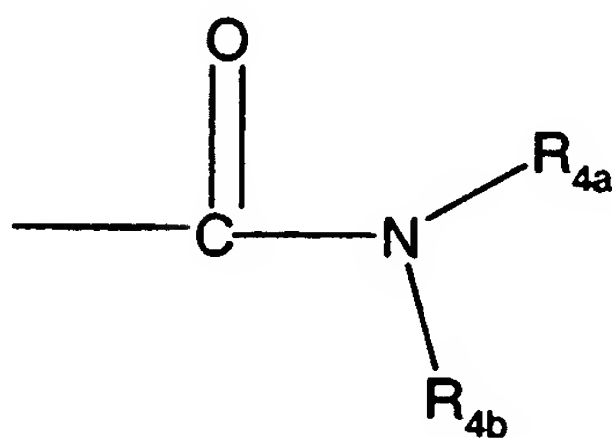


,

where R_{40} is hydrogen or C_1 - C_8 alkyl.

Preferred as the (acylamino acid group) in the group R_4

5 is the group:



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wherein R^{4a} is selected from the group consisting of H,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and
wherein NR^{4b} is an amino acid residue of either a natural
or unnatural amino acid with the nitrogen atom being part
5 of the amino group of the amino acid. A preferred R^{4a}
group is the group hydrogen (H). A preferred source of
amino acid residue is the amino acid group selected from
the group comprising isoleucine, valine, phenylalanine,
aspartic acid, leucine, glycine and isomers and
10 derivatives thereof.

A salt or a prodrug derivative of the (acylamino
acid group) is also a suitable substituent.

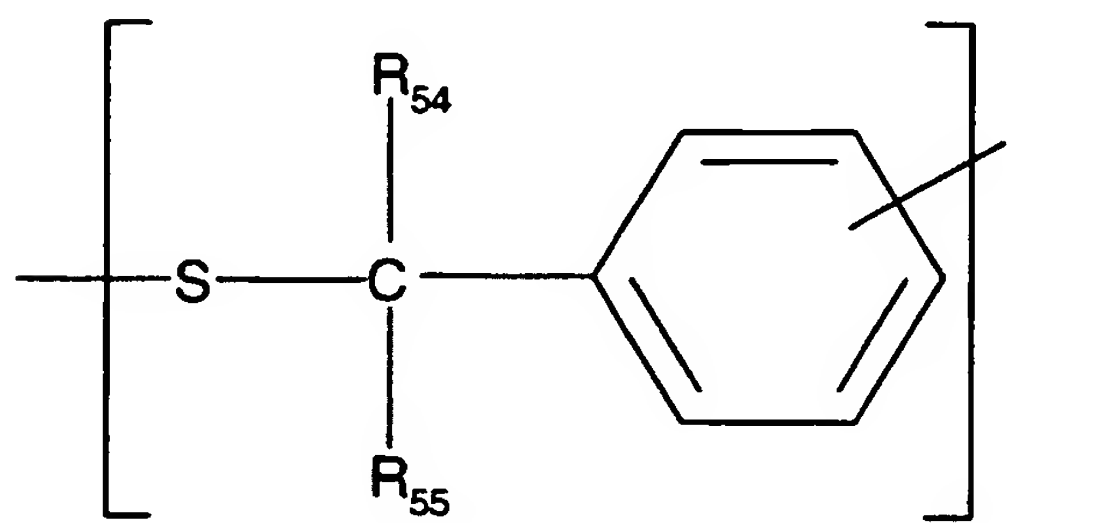
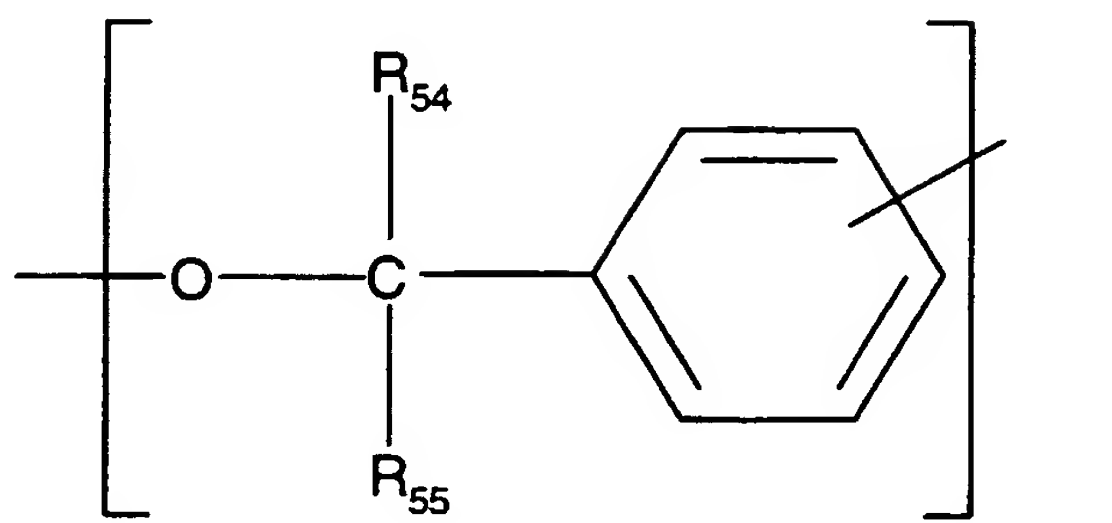
15 Particularly preferred are R^{4b} groups that combine
with the nitrogen atom to represent amino acid groups
selected from: glycine, glycine methyl ester, L-
alanine, L-alanine methylester, L-leucine, L-leucine
methyl ester, L-aspartic acid, L-aspartic acid dimethyl
20 ester, L-phenyl alanine, L-phenylalanine methyl ester,
malonic acid, malonic acid dimethylester, L- valine, L-
valine methyl ester, L-isoleucine, L-isoleucine methyl
ester, or salt, and derivatives thereof.

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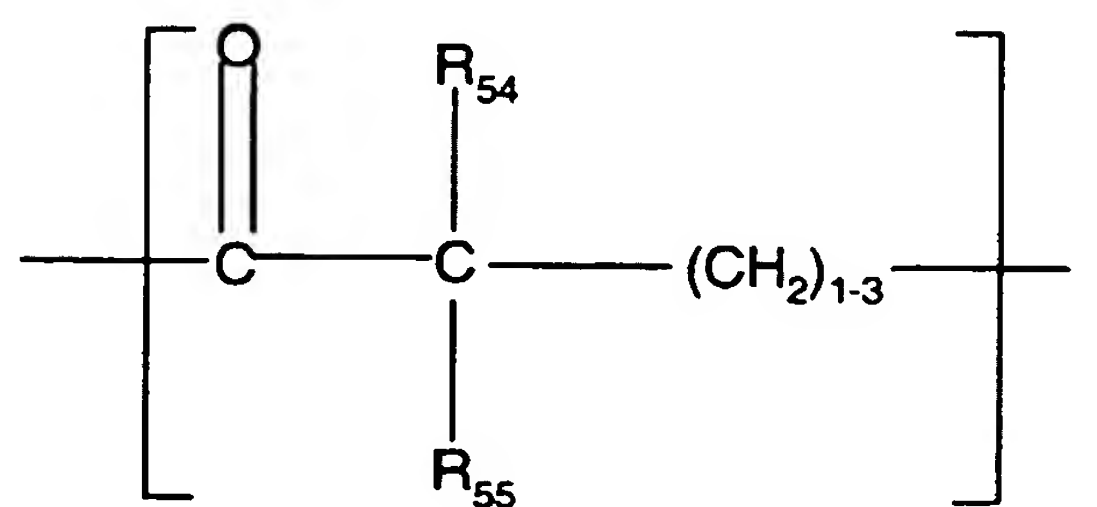
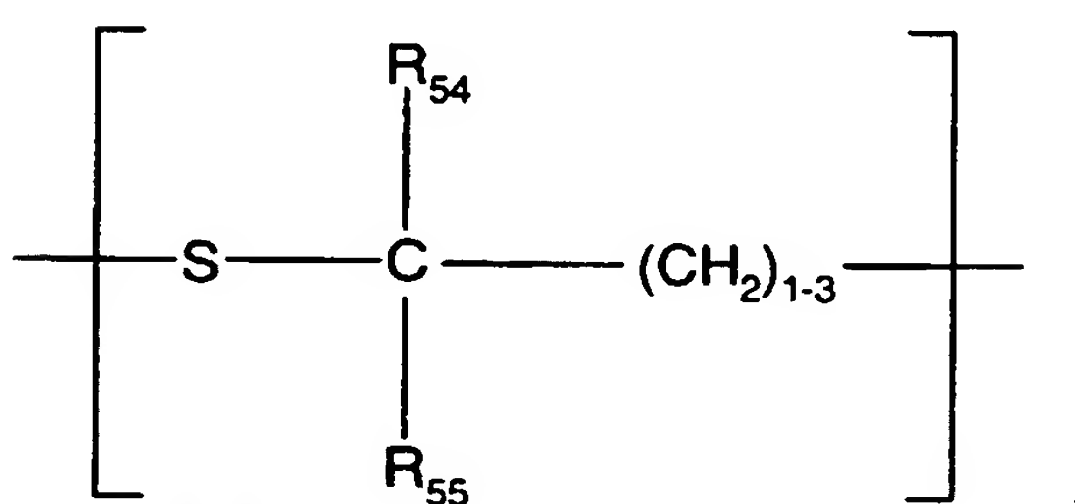
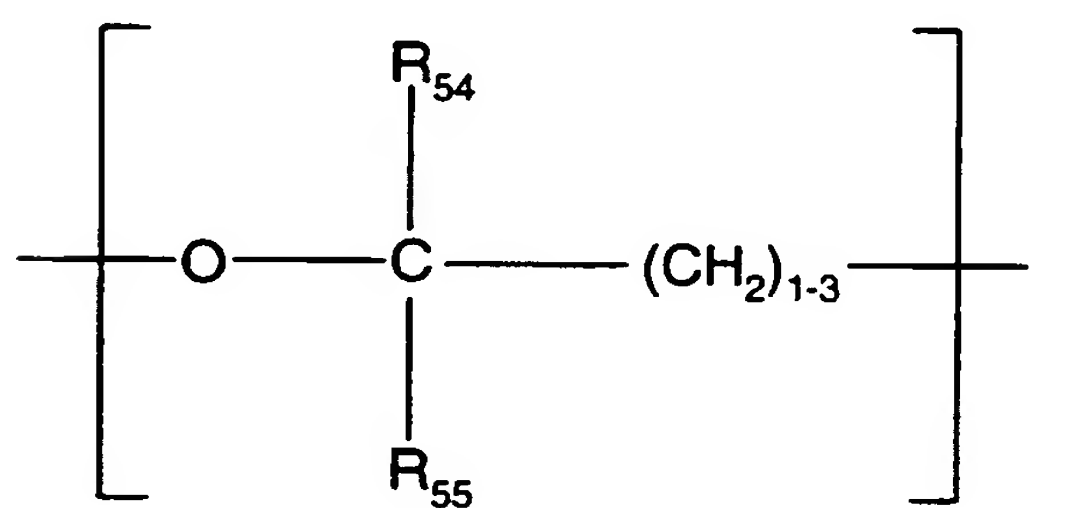
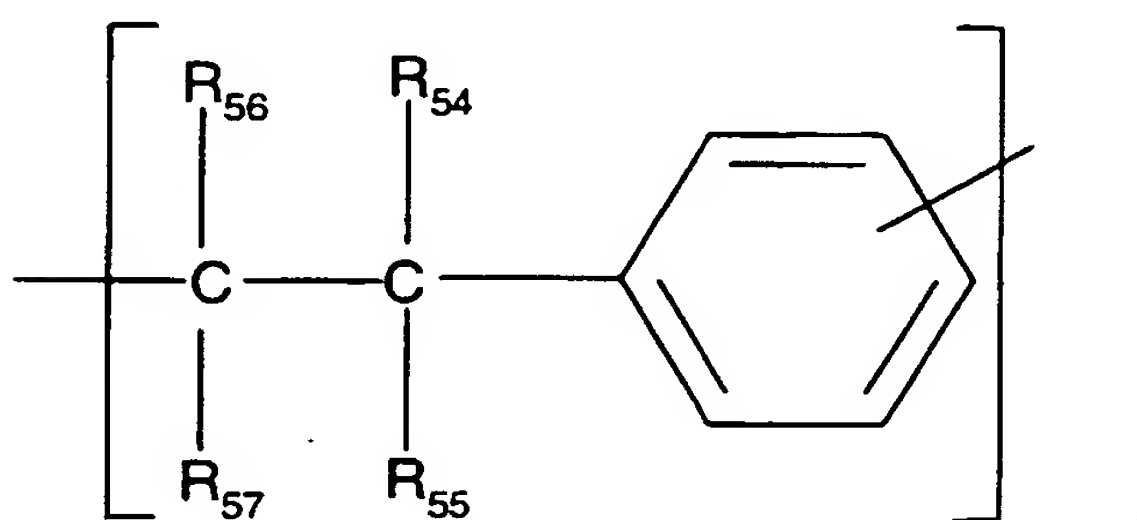
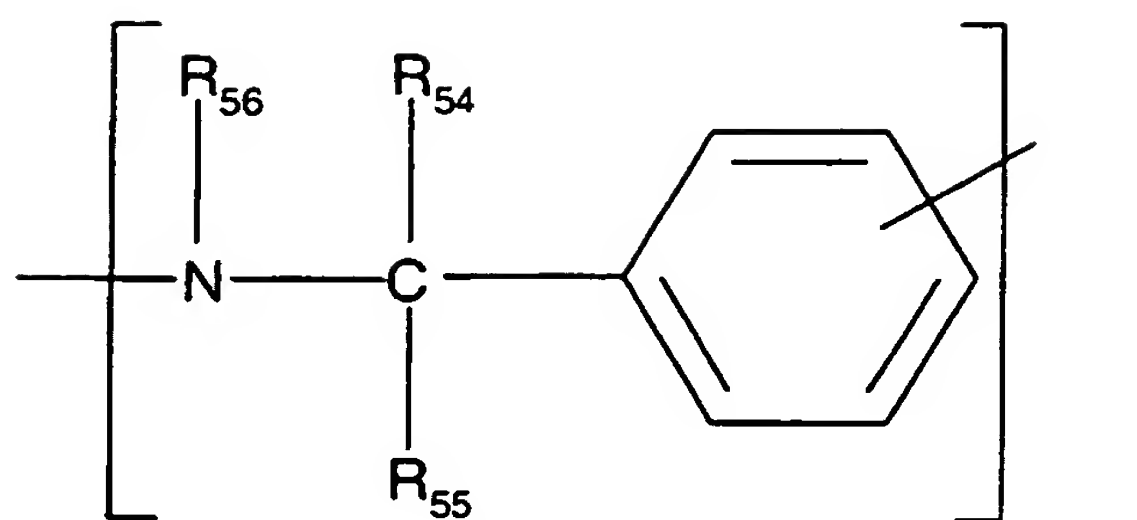
Preferred R₅ Substituents:

Preferred acid linker, -(L_a)-, for R₅ is selected from the group consisting of;

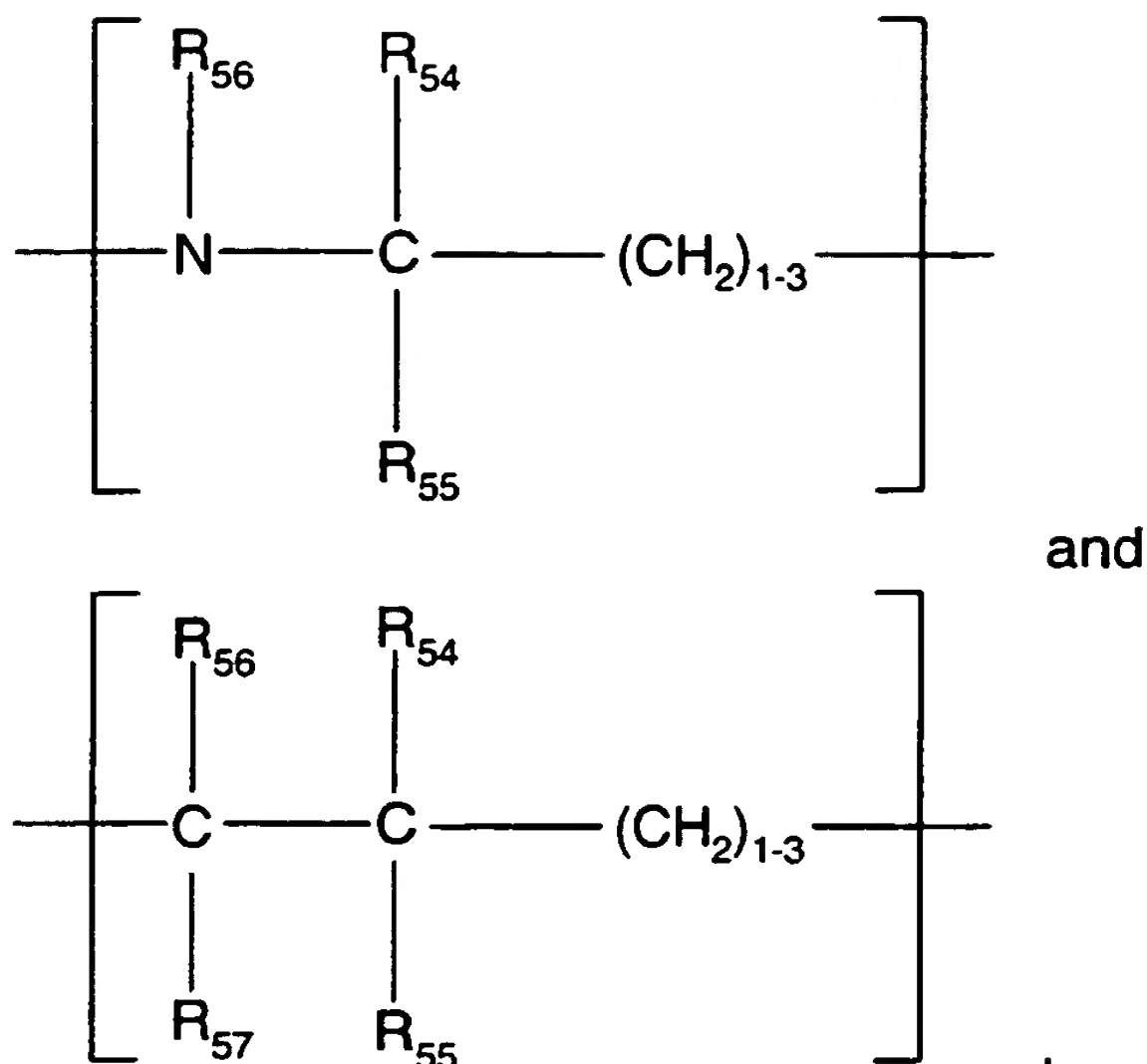
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wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo. Preferred (acidic group) for R₅ is selected from the group consisting of -CO₂H, -SO₃H and -P(O)(OH)₂

Preferred R₆ and R₇ substituents:

Another preferred subclass of compounds of formula (III) are those wherein for R₆ and R₇ the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂

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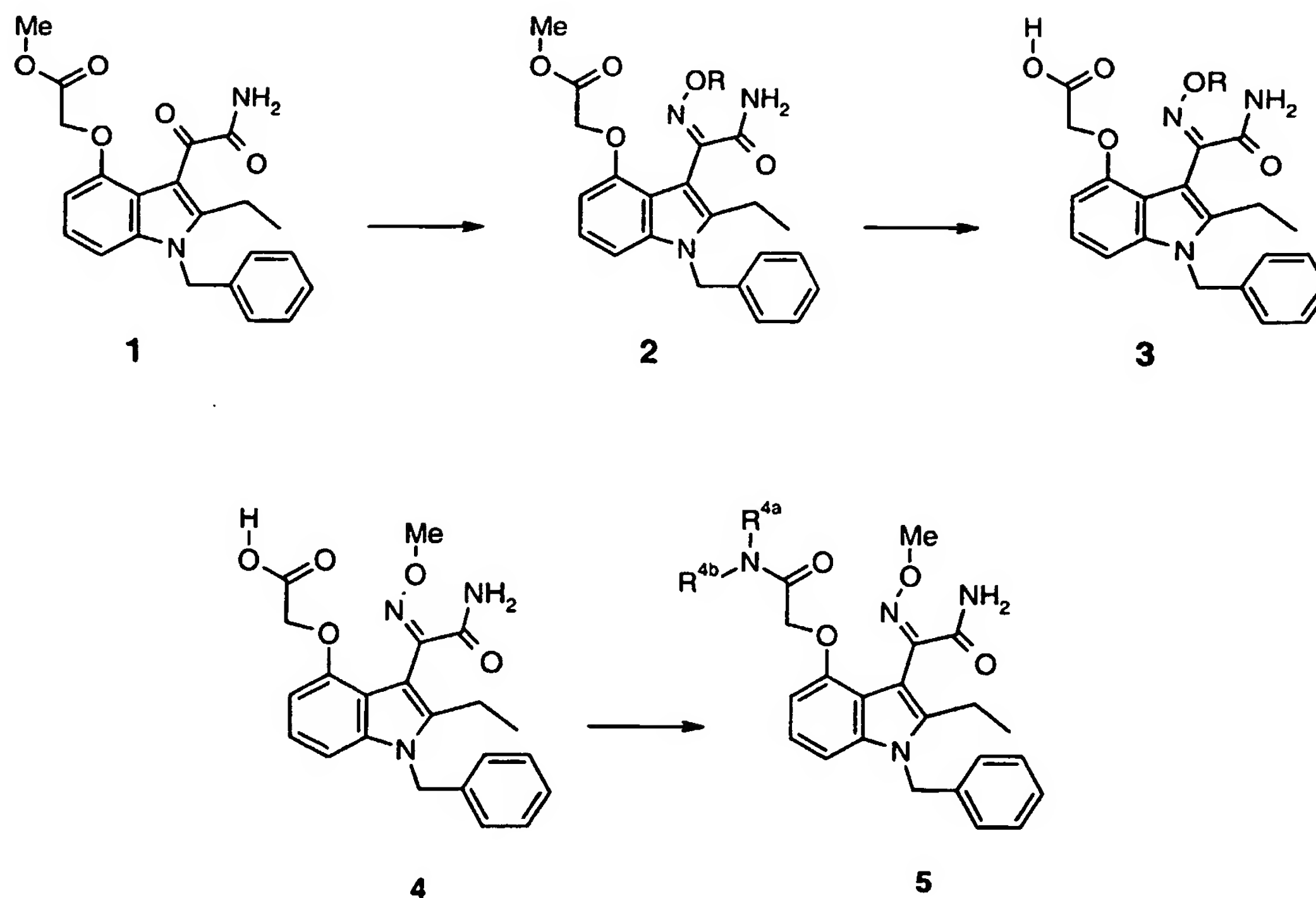
alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂
alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂
alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio,
C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆
5 alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆
haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl,
-C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy,
phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino,
bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H,
10 chloro, cyano, cyanoguanidinyl, fluoro, guanidino,
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,
iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl,
and carbonyl; where n is from 1 to 8.

15 Most preferred as non-interfering substituents are
methyl, ethyl, propyl, and isopropyl.

The indole-3-oxime compounds of the invention can be
prepared following protocol of scheme 2 below;

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Scheme 2



5

To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in scheme 1, compound 1 in scheme 2, *supra.*) is heated with hydroxylamine hydrochloride (when R is H) in a THF/methanol mixture for 8 hours or until the reaction was deemed complete. The reaction product is isolated by chromatography or other known laboratory procedure to afford a white solid. Substituted oximes such as when R is methyl, ethyl, phenyl or other substituent can be prepared by reacting the corresponding substituted hydroxylamine hydrochloride or free base with the

15

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glyoxylamide as described *supra*. The ester functionality at the 4 or 5 position on the indole nucleus, as in for example, compound 2, can be: (a) converted to the acid by hydrolysis using lithium hydroxide or other known ester hydrolysis methods to afford compounds of formula 3, or (b) converted to an amide functionality directly or via the acid functionality to afford compounds of formula 4. General procedures for the conversion of organic acids to amino acid are well known to artisans in the field, and have been documented in general reference texts including, for example, J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989.

15

The oxime acid compounds of formula 3 such as the methyloxime compound such as that of formula 4 can be converted to the corresponding amino acid derivative via the methylester by coupling with various amino acids by general coupling procedures known to one skilled in the art. Additional references, or procedures are found in J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985; R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989 and J. Jones Amino Acids and Peptide

-63-

Synthesis, Oxford Science Publications, Stephen G. Davis, Editor, Oxford University Press Inc., New York, NY, 1992.

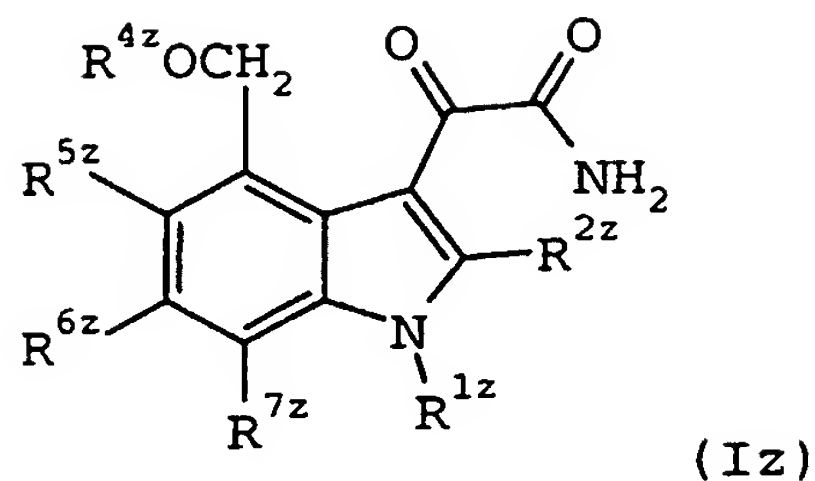
5 **III. Method of Making the 1H-Indole-3-Glyoxylamide Starting Material for Preparing the Compounds of the Invention:**

10 The synthesis of the indole compounds of the invention (viz., Compounds of Formulae I and II) can be accomplished by well known methods as recorded in the chemical literature. In particular, the indole starting materials may be prepared by the synthesis schemes taught in US Patent No. 5,654,326; the disclosure of
15 which is incorporated herein by reference. Another method of making 1H-indole-3-glyoxylamide sPLA₂ inhibitors is described in United States Patent Application Serial No. 09/105381, filed June 26, 1998 and titled, "Process for Preparing 4-substituted 1-H-
20 Indole-3-glyoxylamides" the entire disclosure of which is incorporated herein by reference.

United States Patent Application Serial
No. 09/105381 discloses the following process having
25 steps (a) thru (i):

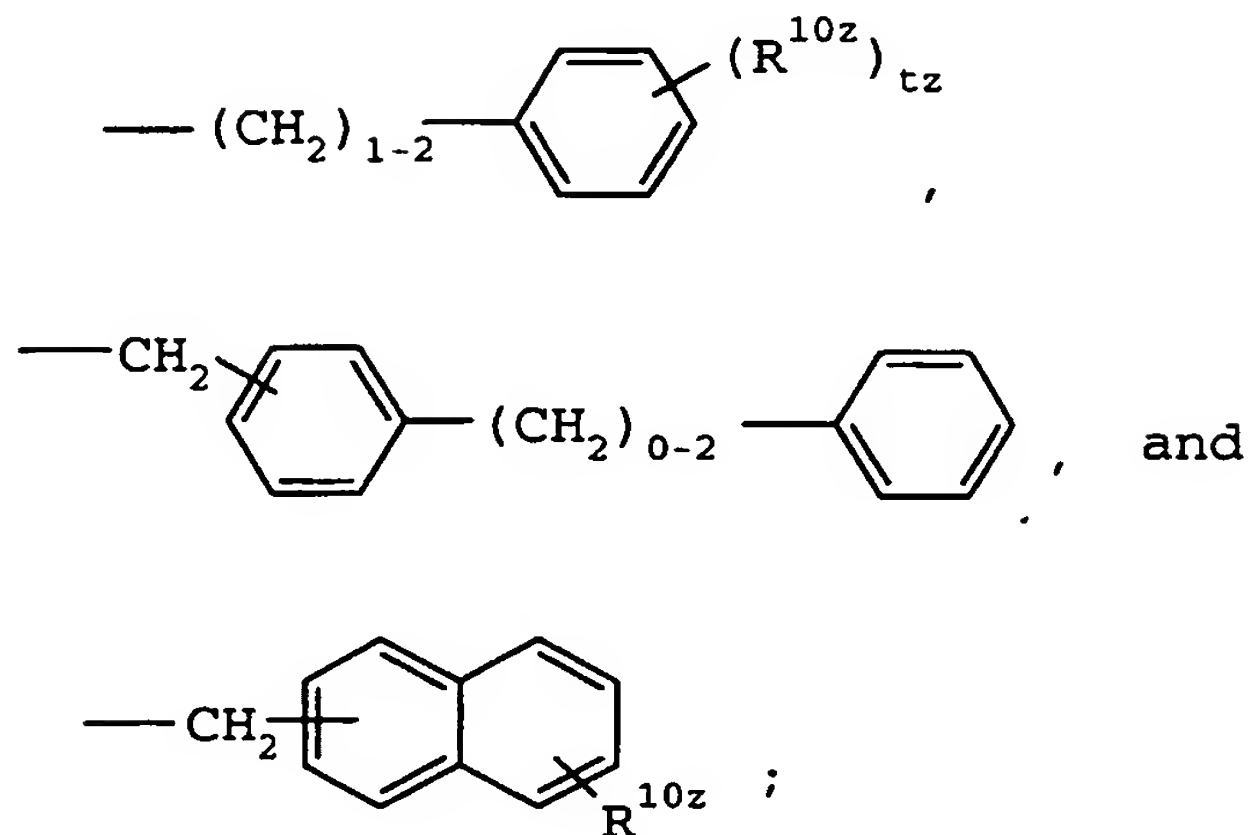
Preparing a compound of the formula (Iz) or a pharmaceutically acceptable salt or prodrug derivative thereof

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5 wherein:

R^{1z} is selected from the group consisting of -C₇-C₂₀ alkyl,



where

10 R^{10z} is selected from the group consisting of halo, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, -S-(C₁-C₁₀ alkyl) and halo(C₁-C₁₀)alkyl, and tz is an integer from 0 to 5 both inclusive;

15 R^{2z} is selected from the group consisting of hydrogen, halo, C₁-C₃ alkyl, C₃-C₄ cycloalkyl, C₃-C₄

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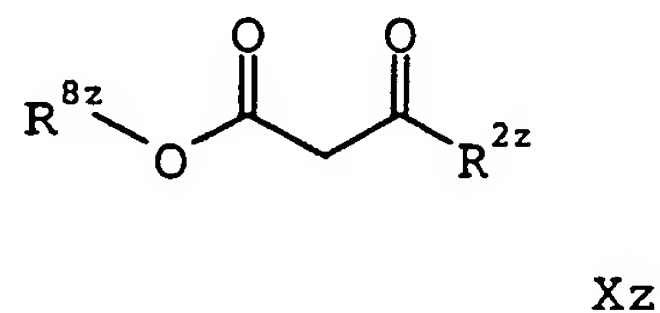
cycloalkenyl, -O-(C₁-C₂ alkyl), -S-(C₁-C₂ alkyl), aryl, aryloxy and HET;

R^{4z} is the group -CO₂H, or salt and prodrug derivative thereof; and

5 R^{5z}, R^{6z} and R^{7z} are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy, halo(C₂-C₆)alkyl, bromo, chloro, fluoro, iodo and aryl;

which process comprises the steps of:

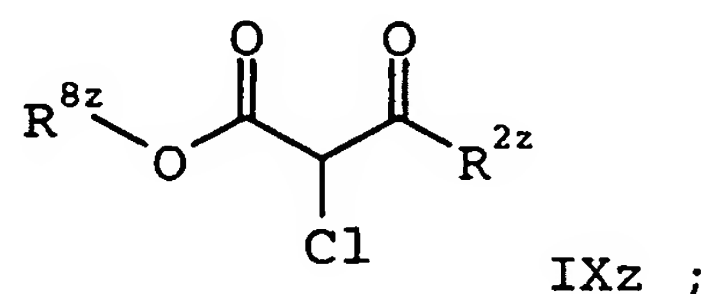
10 a) halogenating a compound of formula Xz



where R^{8z} is (C₁-C₆)alkyl, aryl or HET;

with SO₂Cl₂ to form a compound of formula

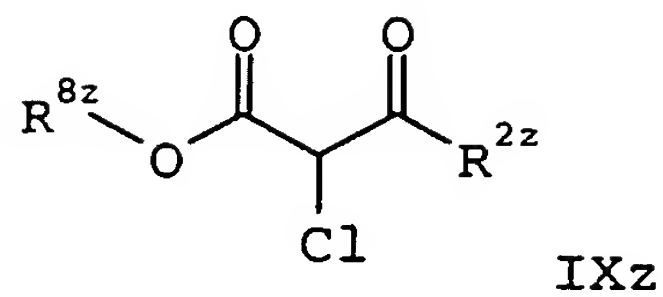
15 IX



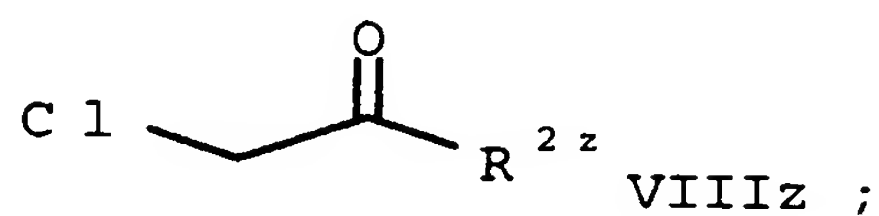
b) hydrolyzing and decarboxylating a compound of formula IXz

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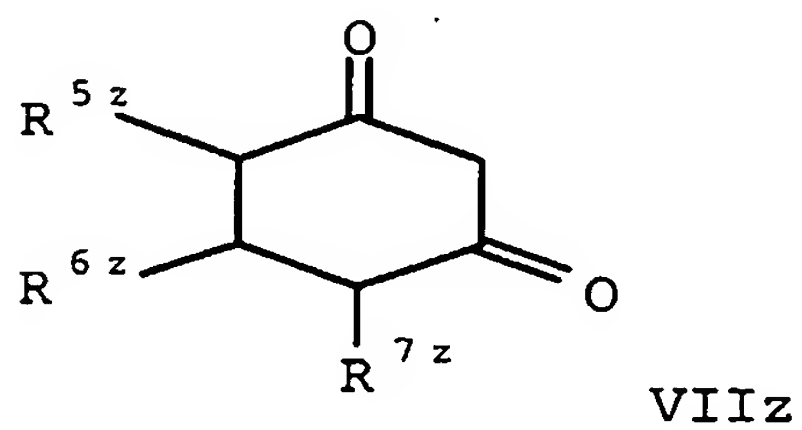
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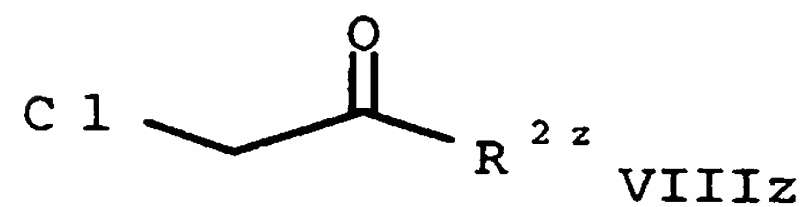
to form a compound of formula VIIIz



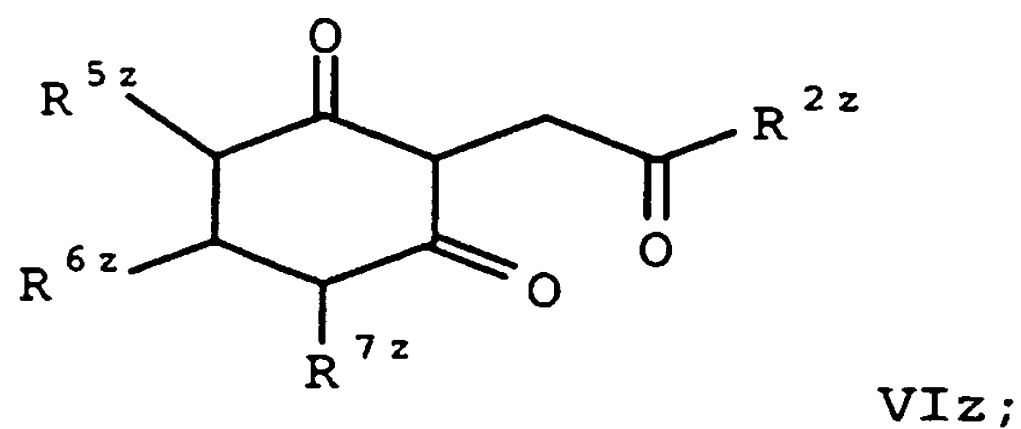
c) alkylating a compound of formula VIIz



10 with a compound of formula VIIIz

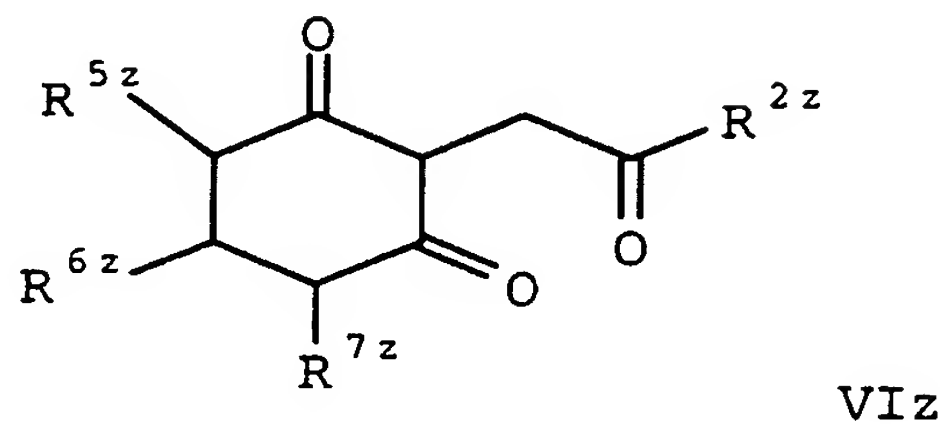


to form a compound of formula VIz



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- d) aminating and dehydrating a compound of formula VIz

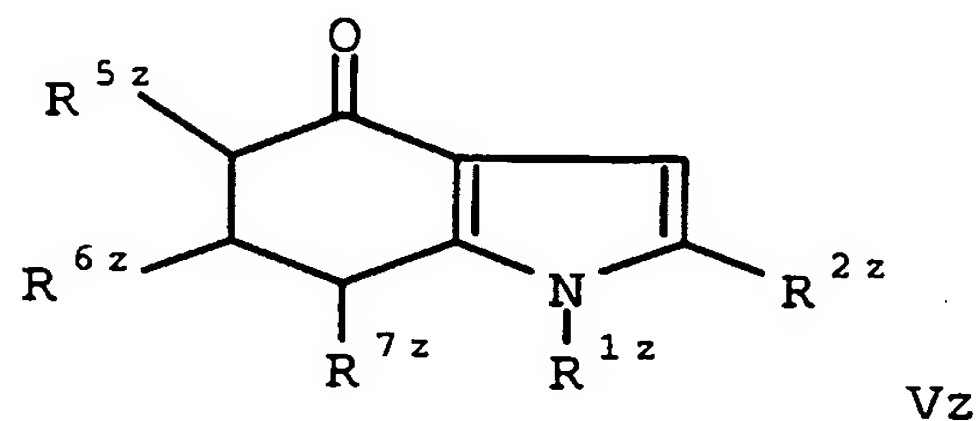


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with an amine of the formula $R^{1z}NH_2$ in the presence of a solvent that forms an azeotrope with water to form a compound of formula Vz;

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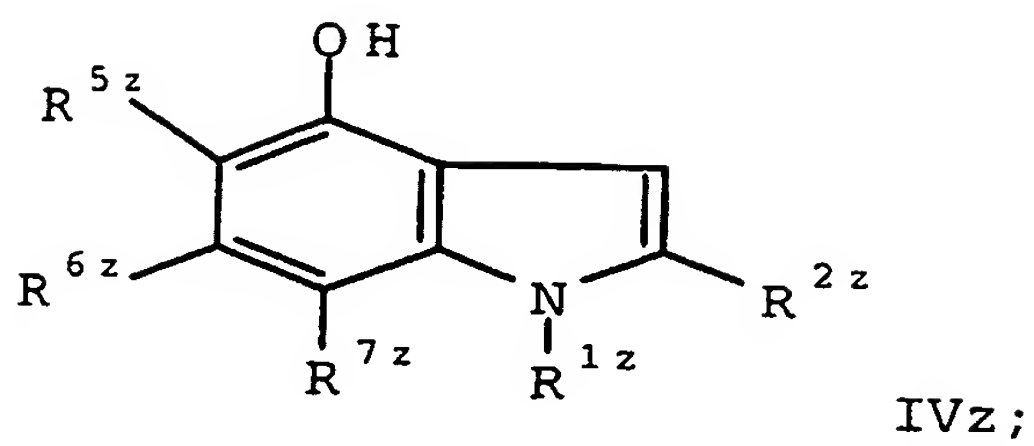
- e) oxidizing a compound of formula Vz



by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IVz

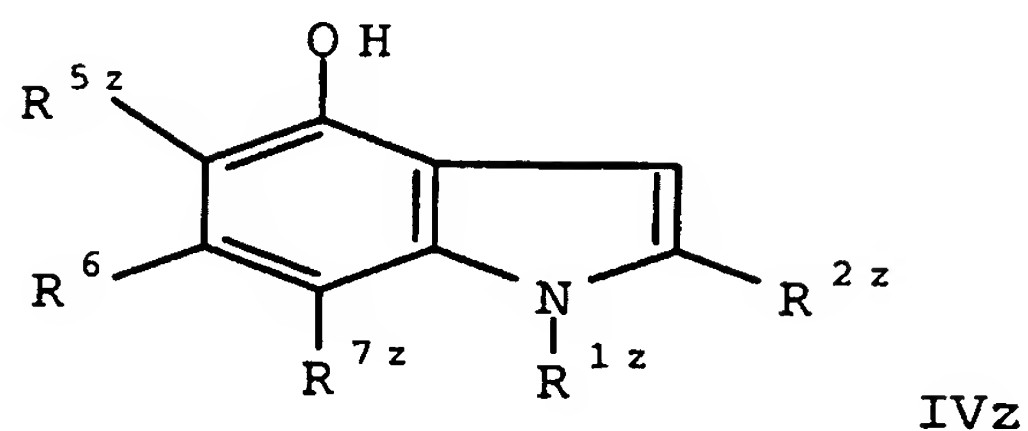
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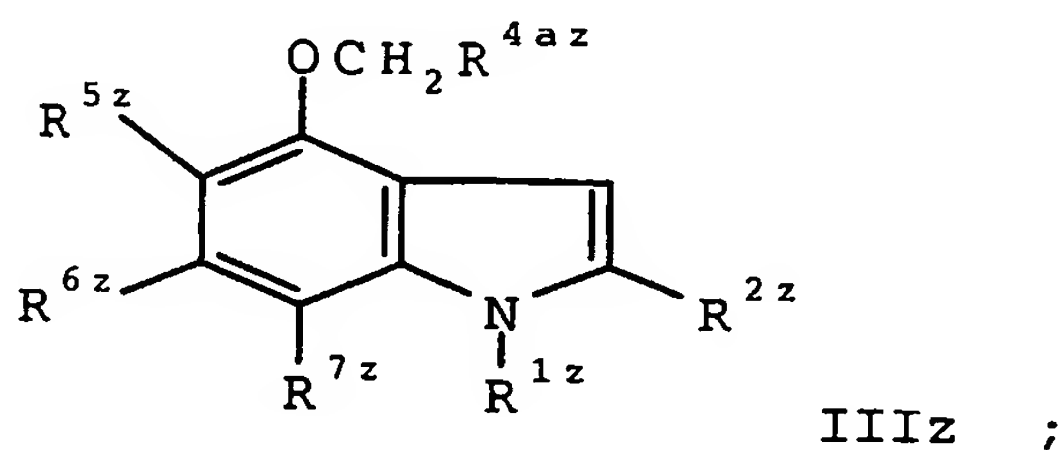


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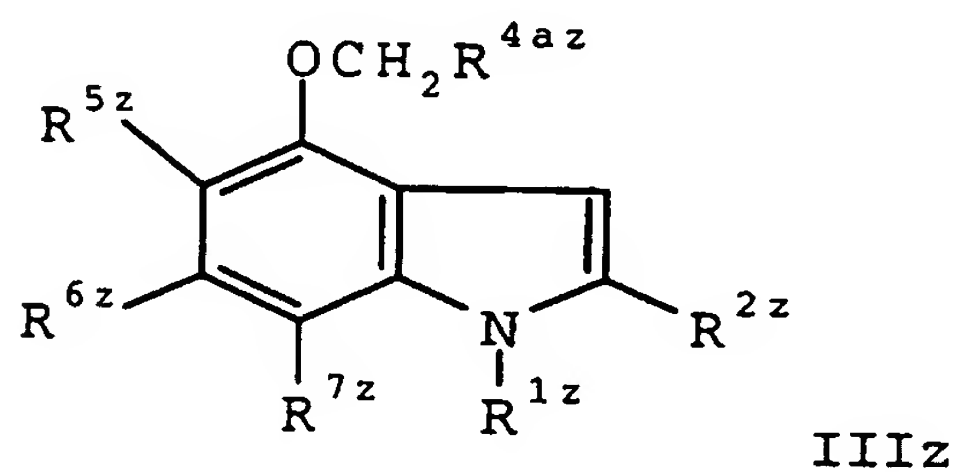
f) alkylating a compound of the formula IVz



with an alkylating agent of the formula XCH_2R^{4az}
 where X is a leaving group and R^{4az} is $-CO_2R^{4b}$,
 where R^{4bz} is an acid protecting group to form a
 compound of formula IIIz

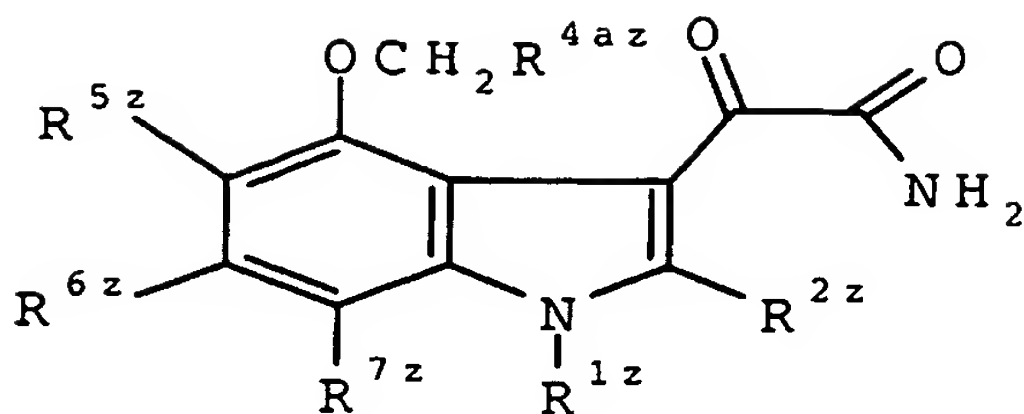


g) reacting a compound of formula IIIz



with oxalyl chloride and ammonia to form a
 compound of formula IIz

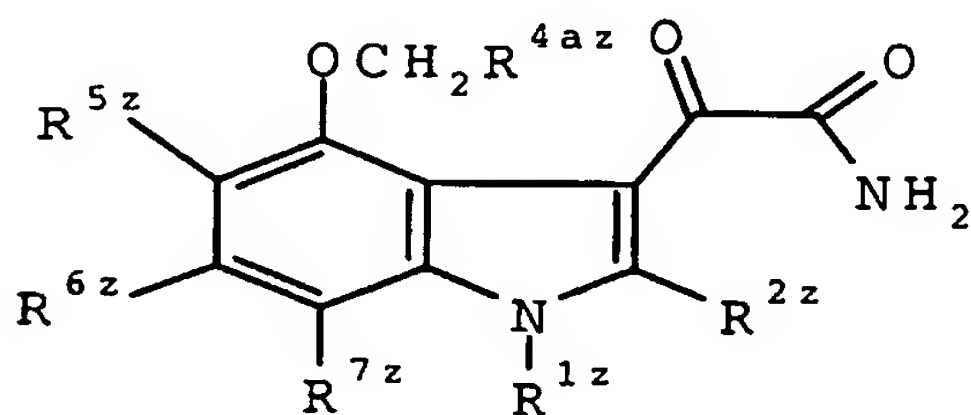
-70-



IIz; and

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- h) optionally hydrolyzing a compound of formula IIz



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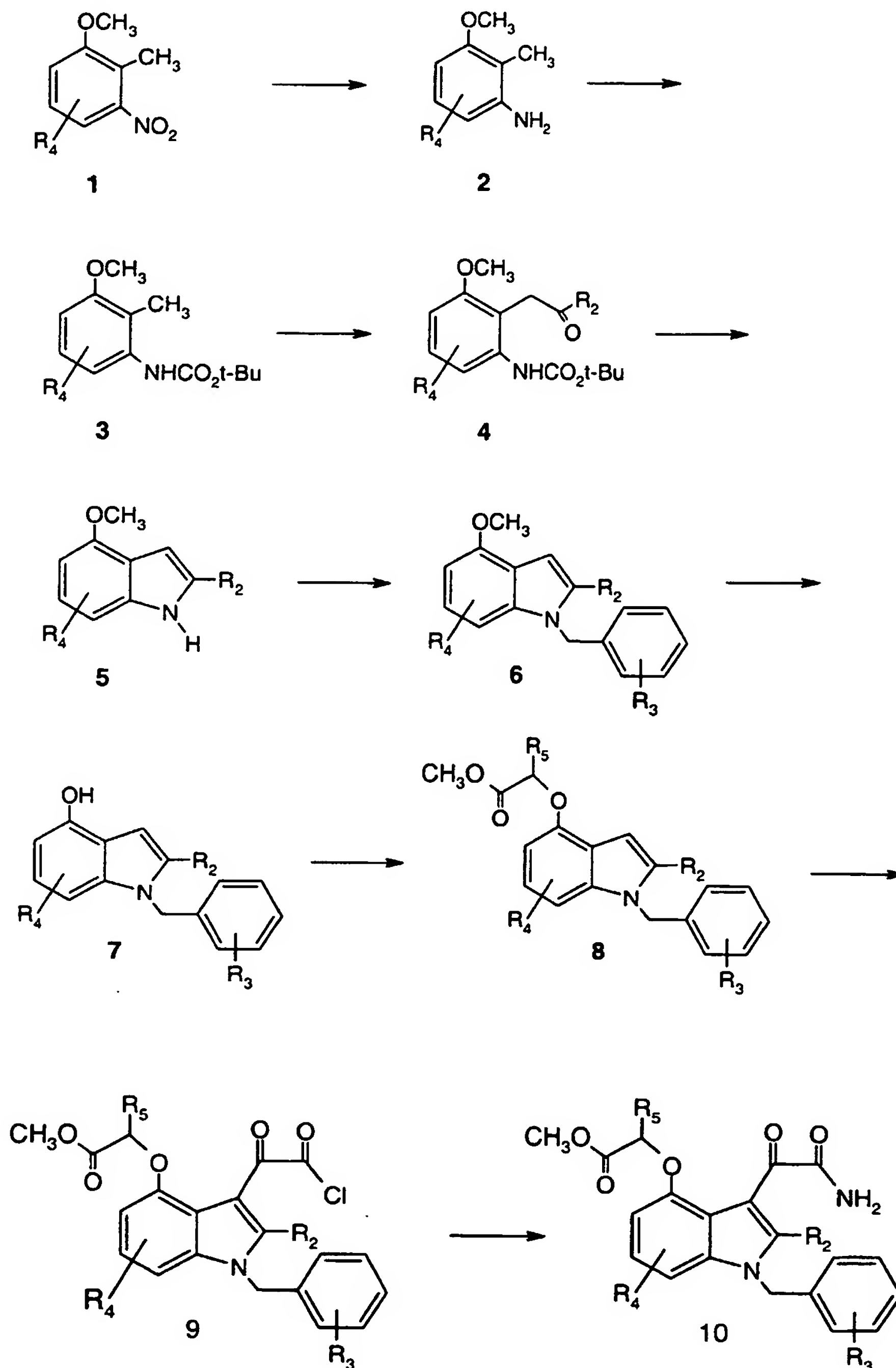
IIz

to form a compound of formula Iz.

An alternative protocol useful for the synthesis of the starting material is shown in Scheme 1 below:

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Scheme 1



5 The synthesis of indole-3-oxime amides (compound of formula I and II, supra.) of this invention uses

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as starting material the glyoxamide ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid methyl ester, compound 10, *supra*. This starting material is prepared as set out in the preceding section or by the method of Example 9 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference).

To obtain the glyoxylamide starting material substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-methoxyaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline 2, obtained, is converted to the N-tert-butyloxycarbonyl derivative 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is

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generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted
5 directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with
10 an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for
15 approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using
20 sodiumhydride as a base, with reaction condition of 5 to 6. The α -[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10.

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Glyoxamide starting material compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is incorporated herein by reference.

IV. Methods of Using the Compounds of the Invention:

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) sPLA₂, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting sPLA₂ mediated release of fatty acids comprises contacting mammalian sPLA₂ with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress

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syndrome, pancreatitis, trauma, bronchial asthma,
allergic rhinitis, rheumatoid arthritis, osteoarthritis,
and related diseases which comprises administering to a
mammal (including a human) a therapeutically effective
5 dose of the indole compound of the invention (see,
formulae I and II).

As previously noted the compounds of this invention
are useful for inhibiting sPLA₂ mediated release of
10 fatty acids such as arachidonic acid. By the term,
"inhibiting" is meant the prevention or therapeutically
significant reduction in release of sPLA₂ initiated
fatty acids by the compounds of the invention. By
"pharmaceutically acceptable" it is meant the carrier,
15 diluent or excipient must be compatible with the other
ingredients of the formulation and not deleterious to
the recipient thereof.

The specific dose of a compound administered
20 according to this invention to obtain therapeutic or
prophylactic effects will, of course, be determined by the
particular circumstances surrounding the case, including,
for example, the compound administered, the route of
administration and the condition being treated. Typical
25 daily doses will contain a non-toxic dosage level of from

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about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I
5 or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of
10 composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The
15 dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and
20 intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention
25 together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical

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formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also

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act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

5 Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or
10 acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

 In powders the carrier is a finely divided solid which is in admixture with the finely divided Active
15 ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active
20 ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium
25 carboxymethyl cellulose, low melting waxes, and cocoa butter.

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Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended
5 in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely
10 divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the
15 scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

20 Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

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Formulation 2

A tablet is prepared using the ingredients below:

	<u>Quantity (mg/tablet)</u>
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

10 An aerosol solution is prepared containing the following components:

	<u>Weight</u>
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

15 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and

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diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

5 Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

10 The Active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and

15 passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each

20 weighing 150 mg.

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Formulation 5

Capsules, each containing 80 mg of Active ingredient,
are made as follows:

5

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The Active ingredient, cellulose, starch, and
magnesium stearate are blended, passed through a No. 45
mesh U.S. sieve, and filled into hard gelatin capsules in
10 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active
ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

15

The Active ingredient is passed through a No. 60 mesh
U.S. sieve and suspended in the saturated fatty acid
glycerides previously melted using the minimum heat
necessary. The mixture is then poured into a suppository
20 mold of nominal 2 g capacity and allowed to cool.

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Formulation 7

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

5

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

10

Formulation 8

15

An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 ml

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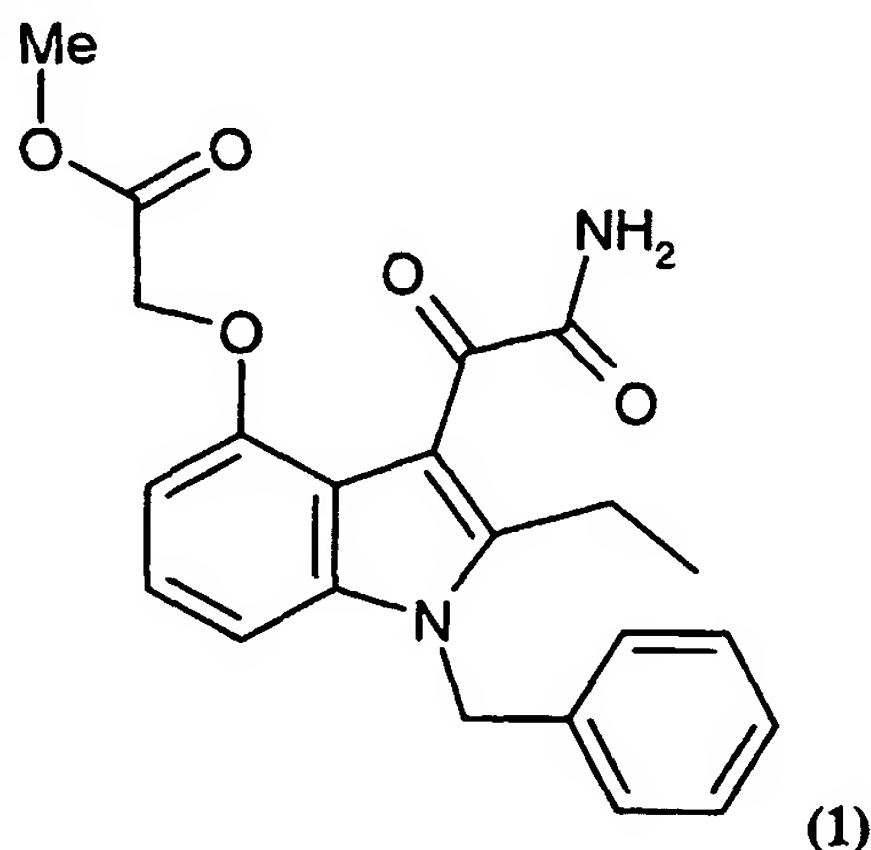
The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

5 All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

10

Example 1

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, a compound represented by the compound of formula (1) formula:



15

Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol)

20

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in 250 mL of THF keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0°C and then the bath replaced. After the temperature had cooled to -60°C, 5 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl. 10 The organic layer was separated, washed with water, brine, dried over MgSO₄, and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of 15 trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried (MgSO₄) and concentrated. The residue was chromatographed three 20 times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for C₁₁H₁₃NO:

Calculated: C, 75.40; H, 7.48; N, 7.99

Found: C, 74.41; H, 7.64; N, 7.97.

25

Part B. Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

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2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL (24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried (MgSO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.

3.1g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M BBr_3 in methylene chloride with stirring at room temperature for 5 hours, followed by concentration at reduced pressure. The residue was dissolved in ethyl acetate, washed with brine and dried (MgSO_4). After concentrating at reduced pressure, the residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.58g (54% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90°C.

Analyses for $\text{C}_{17}\text{H}_{17}\text{NO}$:

Calculated: C, 81.24; H, 6.82; N, 5.57
Found: C, 81.08; H, 6.92; N, 5.41.

Part D. Preparation of [[2-Ethyl-1-(phenylmethyl)-

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1H-indol-4-yl]oxy]acetic acid methyl ester.

2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56g, 6.2 mmol) was added to a mixture of 248mg (6.2 mmol) of 60% NaH/mineral oil in 20mL DMF and stirred for 0.67 hour.

5

Then 0.6 mL(6.2 mmol) of methyl bromoacetate was added and stirring was continued for 17 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with
10 brine, dried (MgSO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane, to give 1.37g (69% yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 89-92°C.

15 Analyses for $\text{C}_{20}\text{H}_{21}\text{NO}_3$:

Calculated: C, 74.28; H, 6.55; N, 4.33

Found: C, 74.03; H, 6.49; N, 4.60.

20 **Part E. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.**

Oxalyl chloride (0.4 mL, 4.2 mmol) was added to 1.36g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester in 10 mL of methylene
25 chloride and the mixture stirred for 1.5 hours. The mixture was concentrated at reduced pressure and residue taken up in 10 mL of methylene chloride. Anhydrous ammonia was bubbled in for 0.25 hours, the mixture stirred

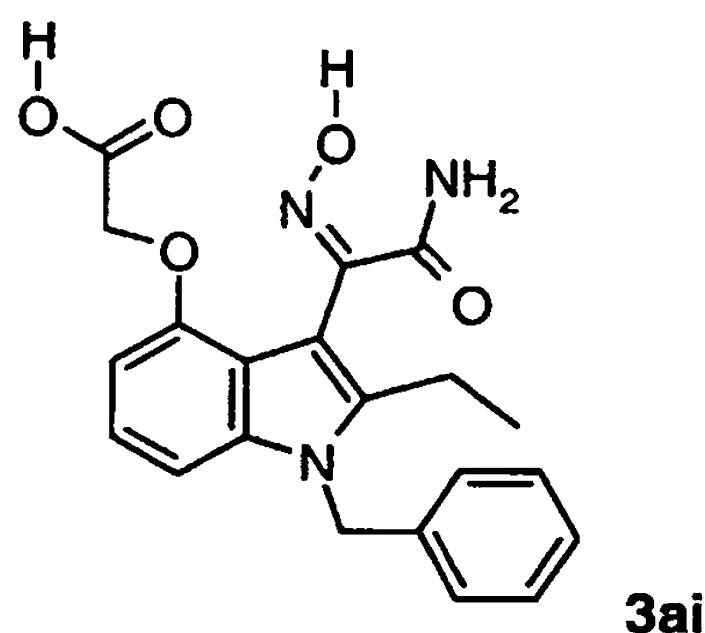
-88-

for 1.5 hours and evaporated at reduced pressure. The residue was stirred with 20 mL of ethyl acetate and the mixture filtered. The filtrate was concentrated to give 1.37g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187°C.

Example 2

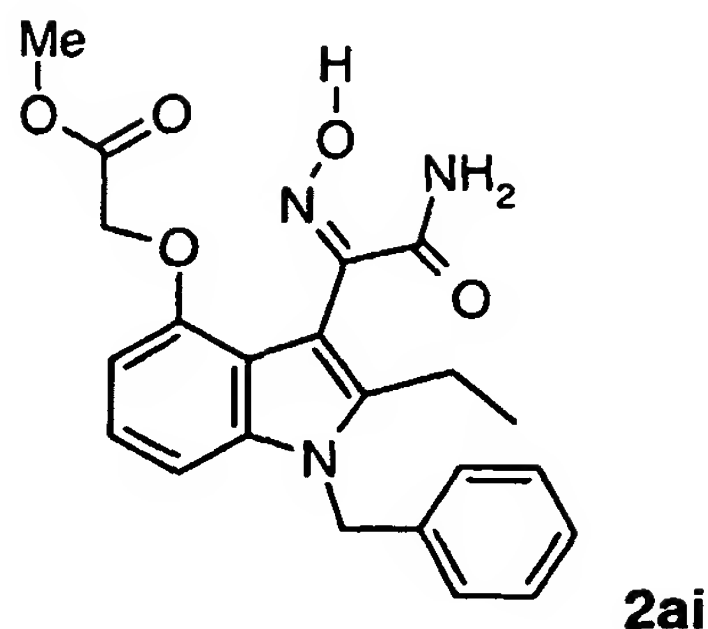
10 (indol-3-oxime amide starting material)

2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.



A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

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A stirred mixture of **1** (600 mg, 1.52 mmol) and hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH₃OH (4 mL) was heated at 55 °C for 8 h. After

5 concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH₂Cl₂) to give the title compound **2ai** (285 mg) as a white solid in 46% yield. IR (CHCl₃) 3510, 3415, 1757, 1667 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.84

10 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.98-7.07 (m, 3H), 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (M⁺+1).

Elemental Analyses for C₂₂H₂₃N₃O₅·0.30(H₂O):

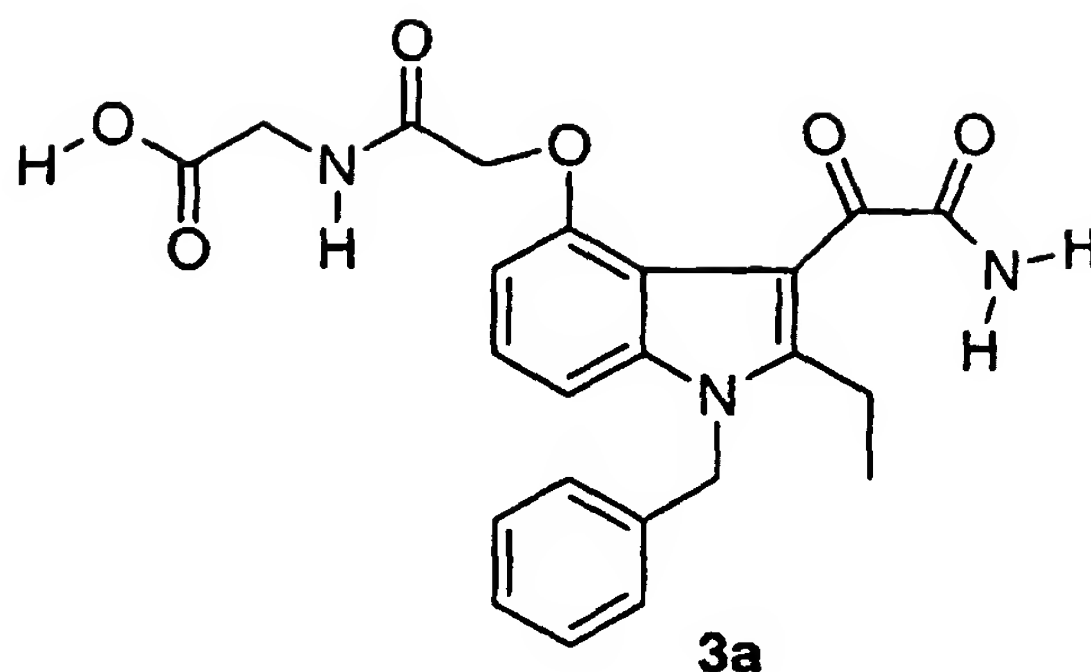
15 Calculated: C, 63.70; H, 5.73; N, 10.13;
 Found: C, 63.68; H, 5.62; N, 10.20.

Example 3

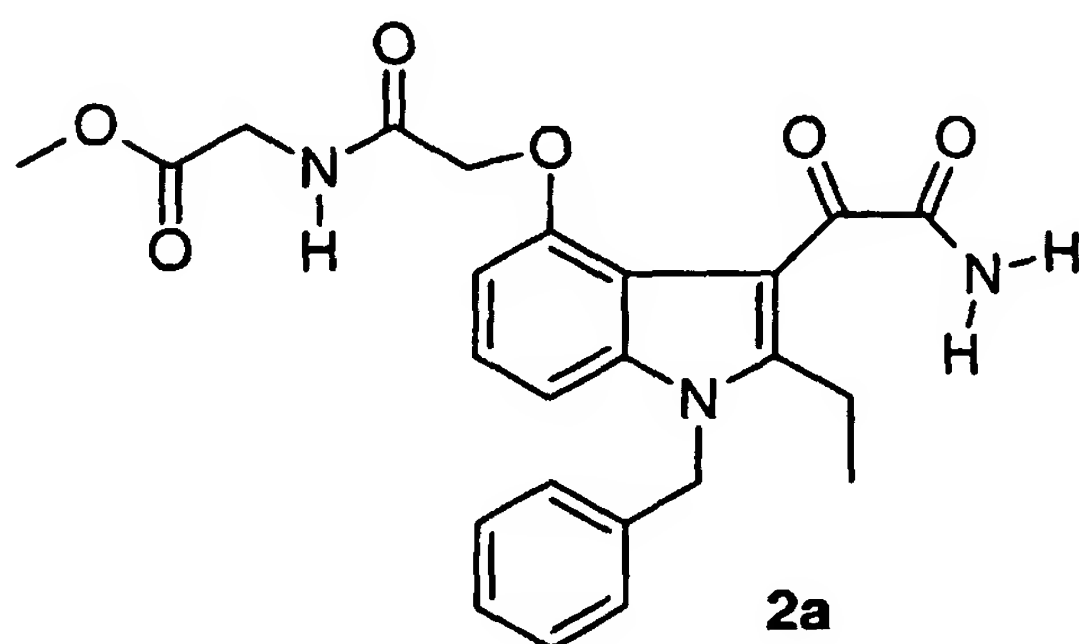
N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-

20 indol-4-yl]oxy]acetyl]glycine

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A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester



5

To a solution of **1** (0.100 g, 0.249 mmol) in 2 mL DMF was added collidine (0.069 mL, 0.523 mmol), methyl glycine hydrochloride (0.0313 g, 0.249 mmol), and benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.115 g, 0.261) sequentially at room temperature. After 2.5 hrs. the reaction mixture was concentrated in vacuo to near dryness, then it was taken up in CH₂Cl₂, chromatographed on a silica gel column (gradient 20-40% THF in CH₂Cl₂) and dried in an 80°C vacuum oven to give 0.0768 g of **2a** as a yellow solid in 68% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 6.8 Hz, 3H), 2.90 (br q, J = 6.8 Hz, 2H),

10

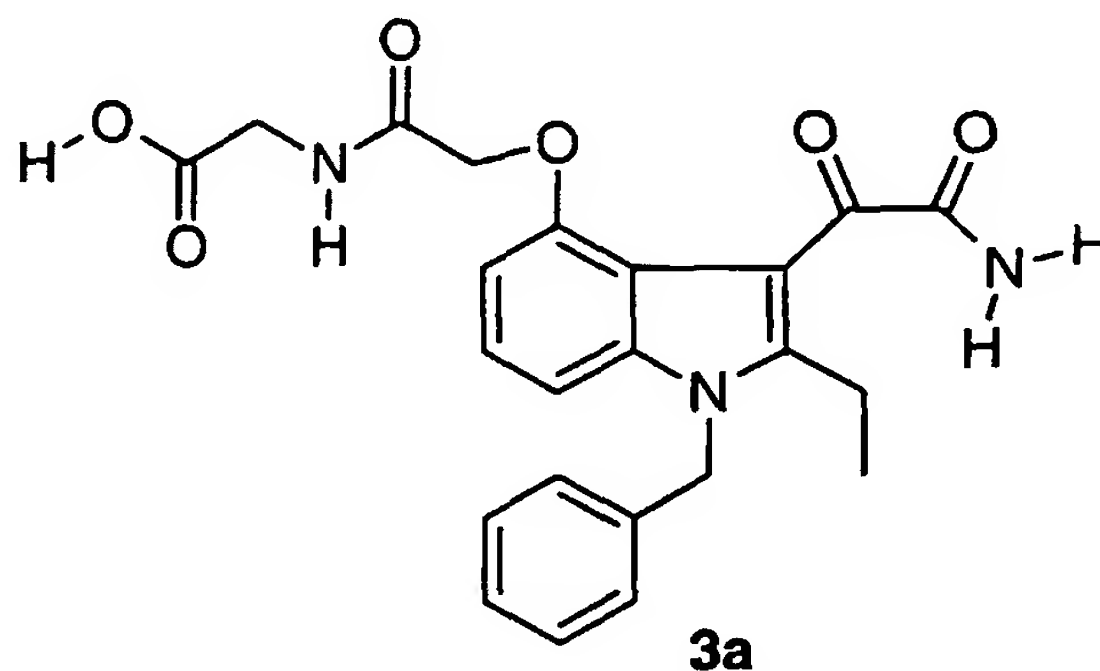
15

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3.57 (s, 3H), 3.88 (d, $J = 5.5$ Hz, 2H), 4.57 (s, 2H), 5.51 (s, 2H), 6.59 (d, $J = 5.6$ Hz, 1H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t, $J = 5.5$ Hz, 1H).

5

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine



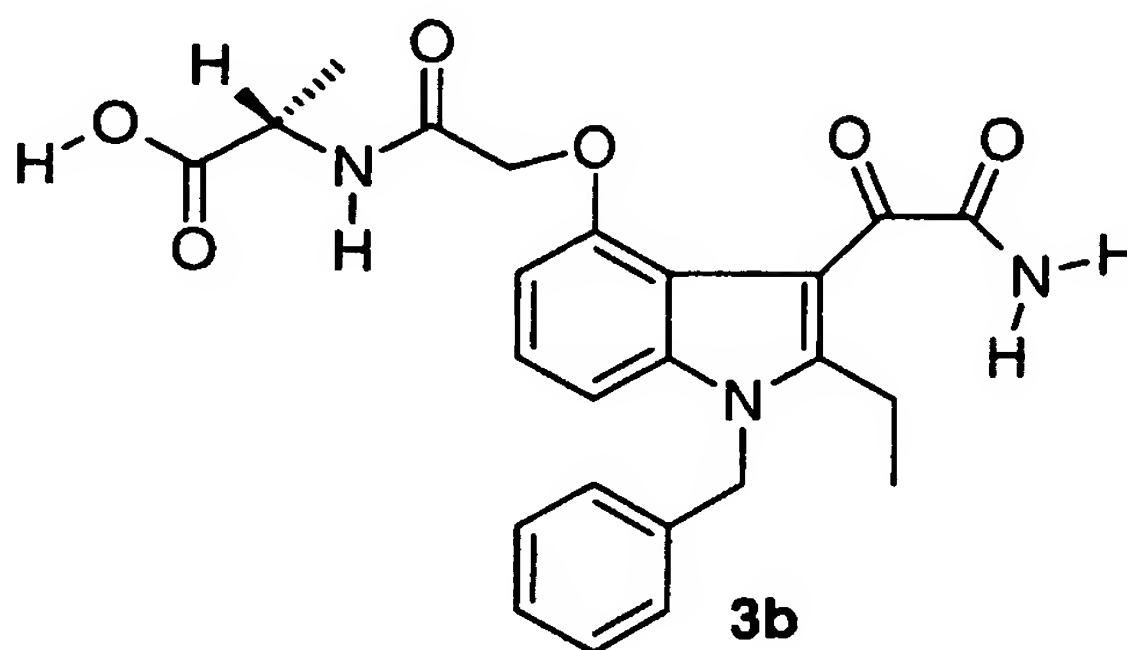
10 To a solution of 2a (0.035 g, 0.078 mmol) in 1 mL THF, 1 mL MeOH and 0.25 mL distilled H₂O was added 4.17N LiOH (0.093 mL, 0.388 mmol) at room temperature. After 2 hrs. the reaction mixture was acidified with 5N HCl (0.093 mL, 0.465 mmol) and concentrated *in vacuo*. The residue
15 was taken up in CH₂Cl₂, then rapidly triturated with hexanes to give a yellow suspension which was filtered and dried in an 80°C vacuum oven to give 0.0336 g of 3a as a yellow solid in 99% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, $J = 5.9$ Hz, 3H), 2.90 (br q, $J = 5.9$ Hz, 2H), 3.80 (d, $J = 4.8$ Hz, 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, $J = 5.8$ Hz, 1H),
20 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, $J = 5.8$ Hz, 1H),

-92-

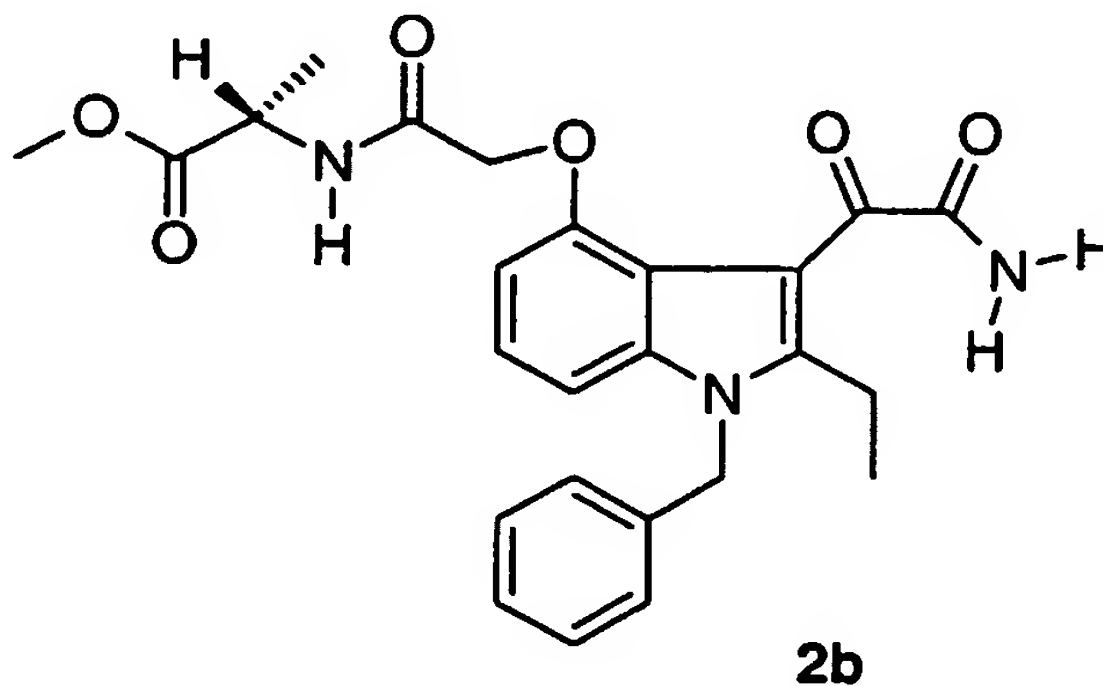
7.01-7.28 (m, 7H), 7.54 (s, 1H), 7.99 (s, 1H), 8.31 (t, J = 4.8 Hz, 1H), 12.25-12.75 (br s, 1H).

Example 4

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine



A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester
10 methyl ester



Following the experimental procedure as described for 2a, 2b was obtained as a yellow solid in 65% yield.

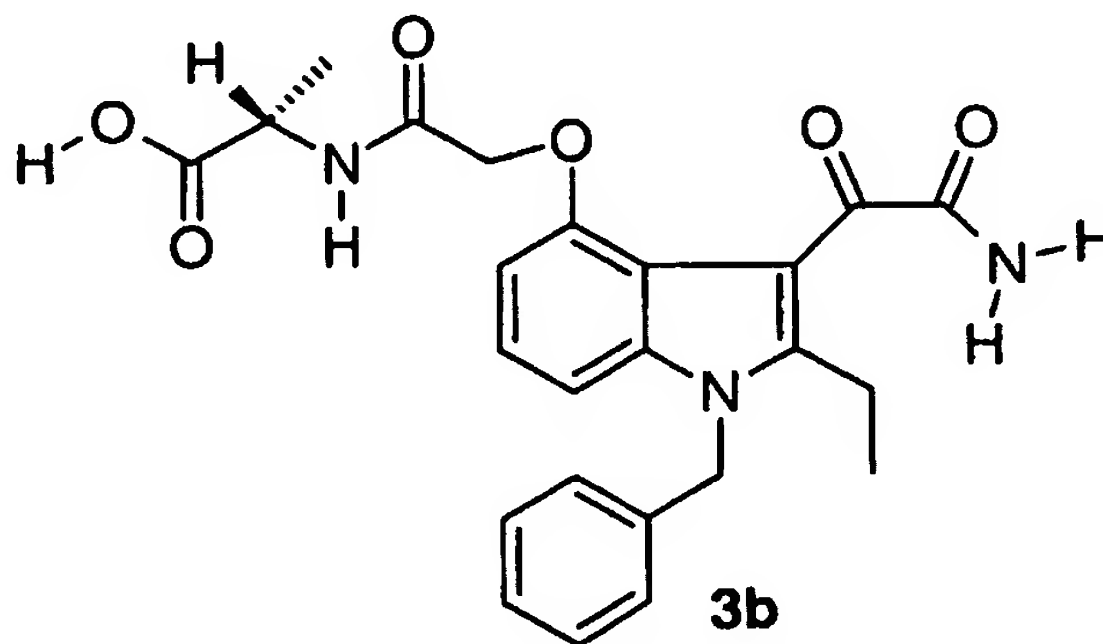
¹H NMR (DMSO-*d*₆) δ 1.04 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 7.3 Hz, 3H), 2.91 (br q, J = 7.2 Hz, 2H), 3.54 (s, 3H), 4.29 (qd, J = 7.3, 6.8 Hz, 1H), 4.55 (s, 2H), 5.51 (s,

15

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2H), 6.57 (m, 1H), 6.99 (d, $J = 7.4$ Hz, 2H), 7.07-7.08 (m, 2H), 7.21-7.31 (m, 3H), 7.56 (s, 1H), 8.05 (s, 1H), 8.40 (d, $J = 6.8$ Hz, 1H).

5 **B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine**

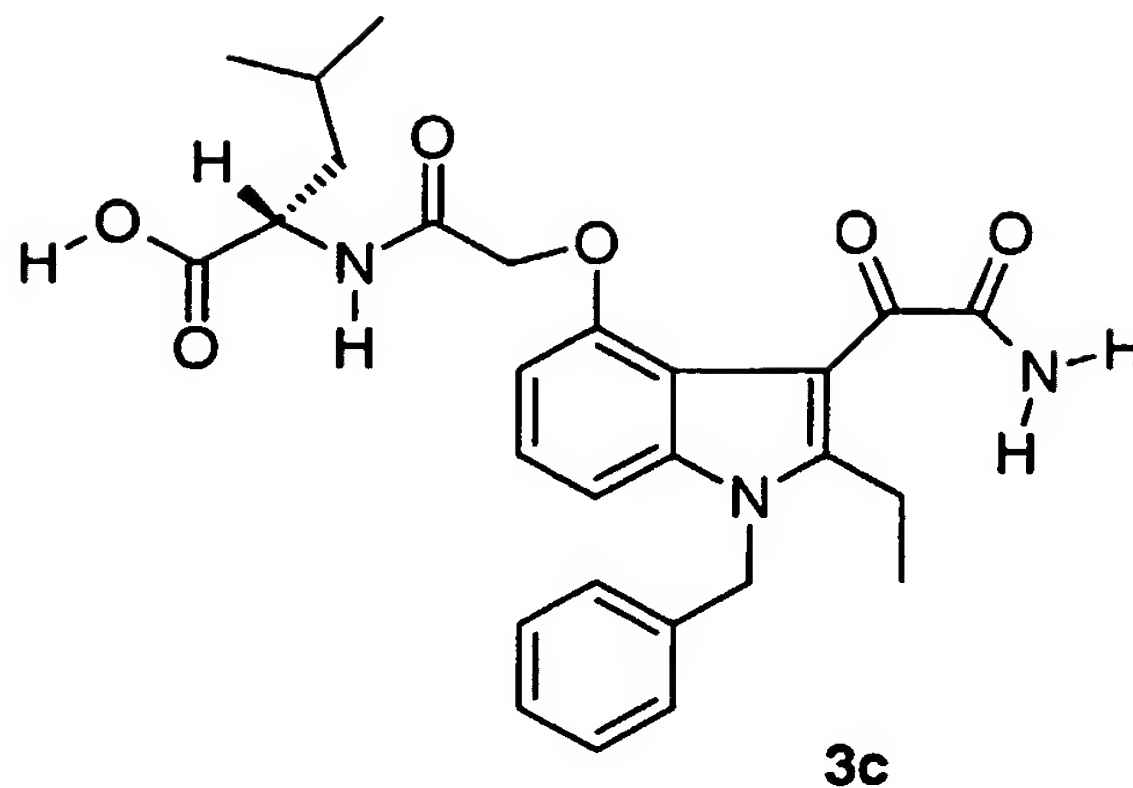


Following the experimental procedure as described for
 10 preparing compound 3a, compound 3b, was obtained as a
 yellow solid in 89% yield. ^1H NMR (DMSO- d_6) δ 1.04 (t, J
 $= 7.2$ Hz, 3H), 1.29 (d, $J = 7.3$ Hz, 3H), 2.91 (br q, $J =$
 7.2 Hz, 2H), 4.22 (td, $J = 7.2, 7.1$ Hz, 1H), 4.54 (s, 2H),
 5.51 (s, 2H), 6.60 (d, $J = 6.3$ Hz, 1H), 7.00-7.09 (m, 4H),
 15 7.21-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.31 (d, J
 $= 7.1$ Hz, 1H), 12.75-12.84 (br s, 1H).

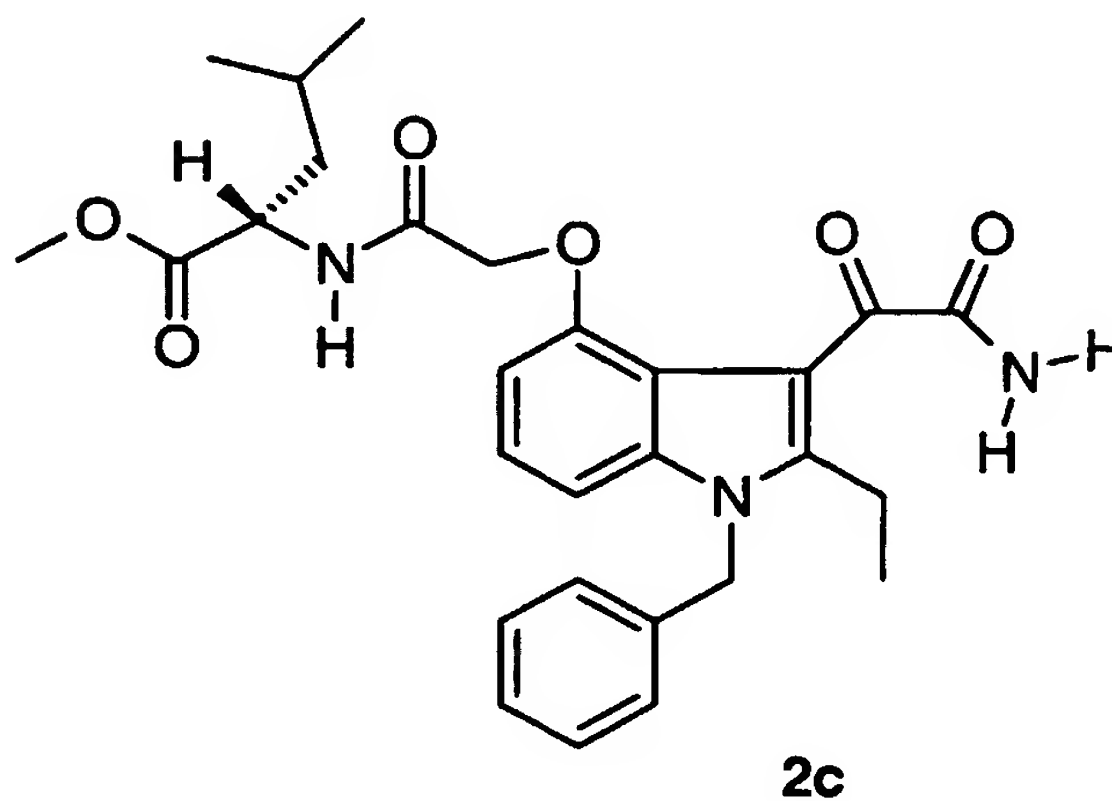
Example 5

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
 20 indol-4-yl]oxy]acetyl]-L-leucine

-94-



A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester

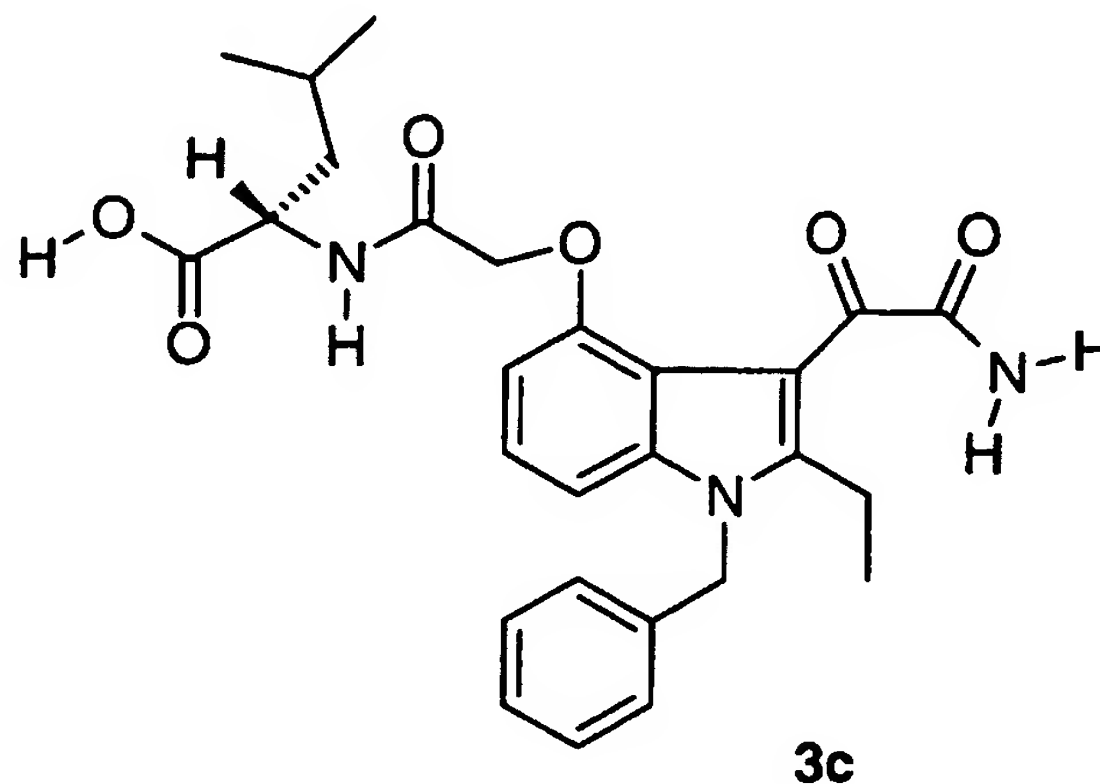


5 Following the experimental procedure as described for 2a, 2c was obtained as a yellow solid in 98% yield. ¹H NMR (DMSO-d₆) δ 0.67 (d, *J* = 5.5 Hz, 3H), 0.72 (d, *J* = 5.7 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.51-1.64 (m, 1H), 2.91 (br q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 4.20-4.27 (m, 1H), 4.57 (s, 2H), 5.52 (s, 2H), 6.53-6.56 (m, 1H), 6.97-7.08 (m, 4H), 7.21-7.29 (m, 3H), 7.56 (s, 1H), 8.07 (s, 1H), 8.37 (d, *J* = 7.3 Hz, 1H).

10

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B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine



5 Following the experimental procedure as described for 3a, 3c was obtained as a yellow solid in 75% yield. ¹H NMR (DMSO-d₆) δ 0.76 (d, *J* = 5.7 Hz, 3H), 0.78 (d, *J* = 6.1 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.39-1.43 (m, 1H), 1.69 (t, *J* = 7.3 Hz, 2H), 2.96 (br q, *J* = 7.3 Hz, 2H), 4.57-4.65

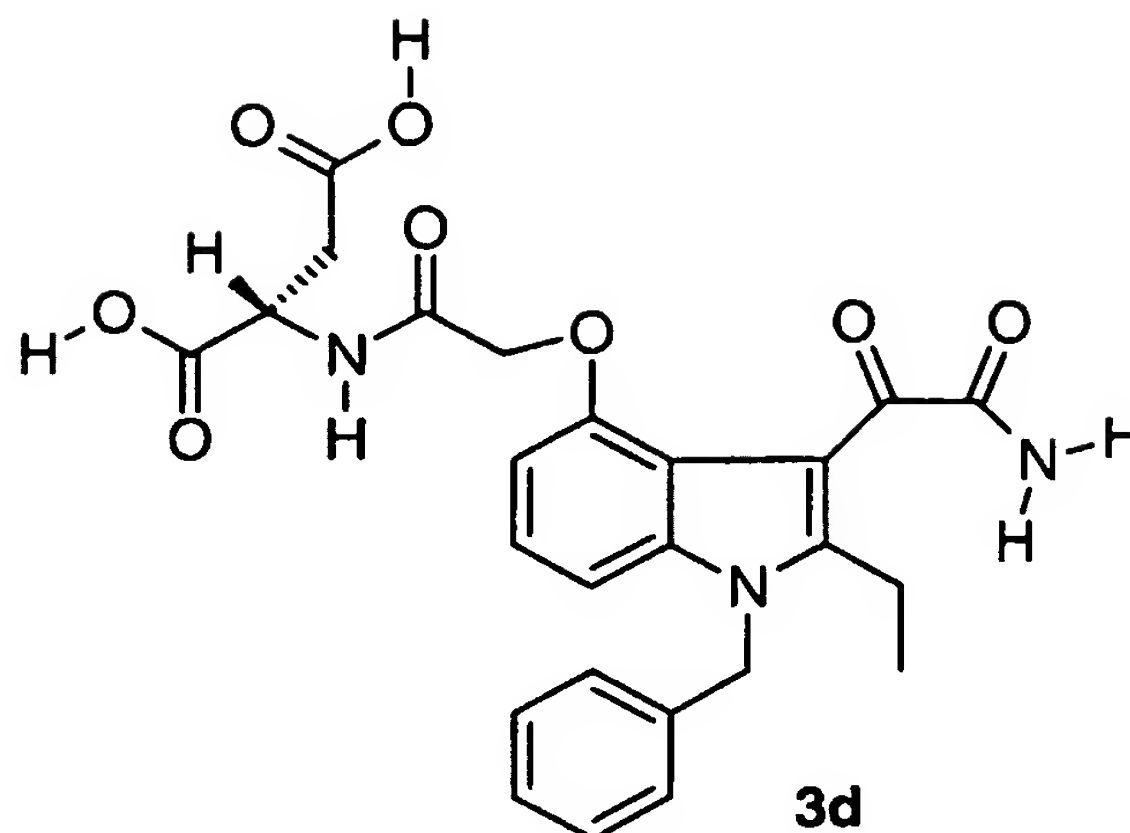
10 (m, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 5.38 (s, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.95-7.12 (m, 5H), 7.26-7.32 (m, 3H), 8.17 (d, *J* = 8.2 Hz, 1H).

15

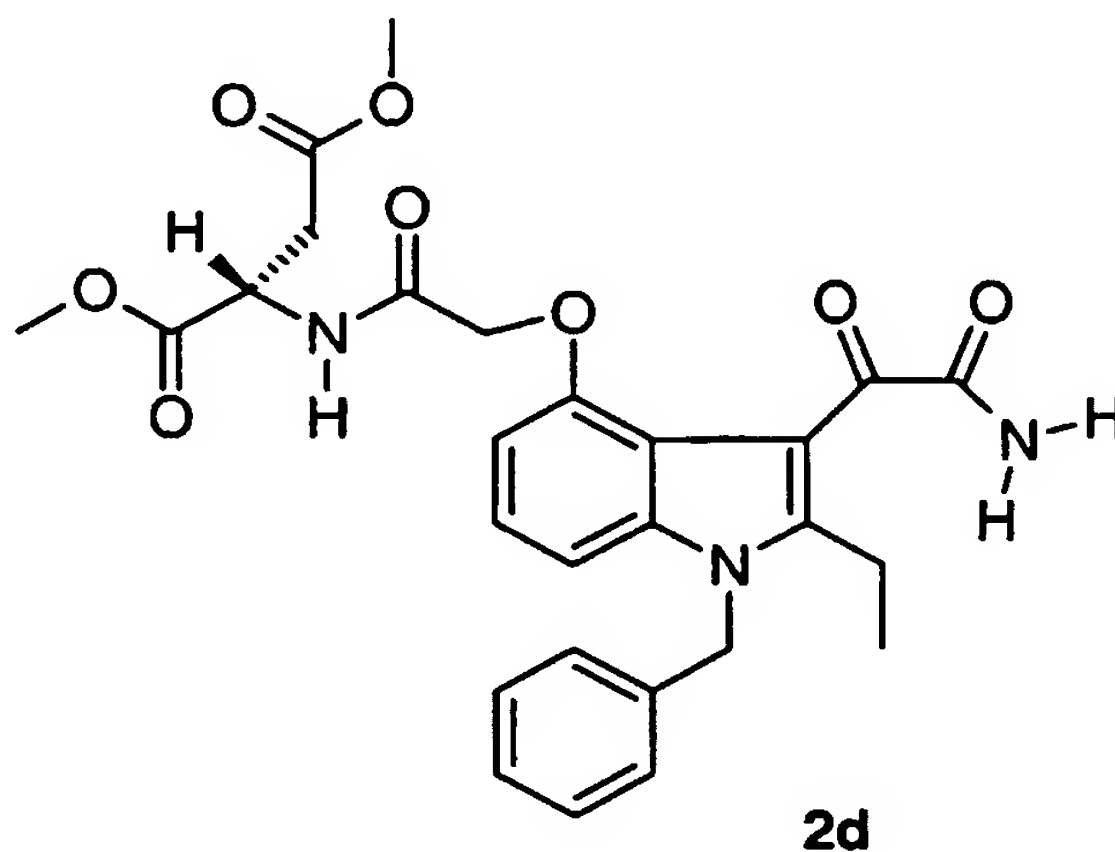
Example 6

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid

-96-



A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester

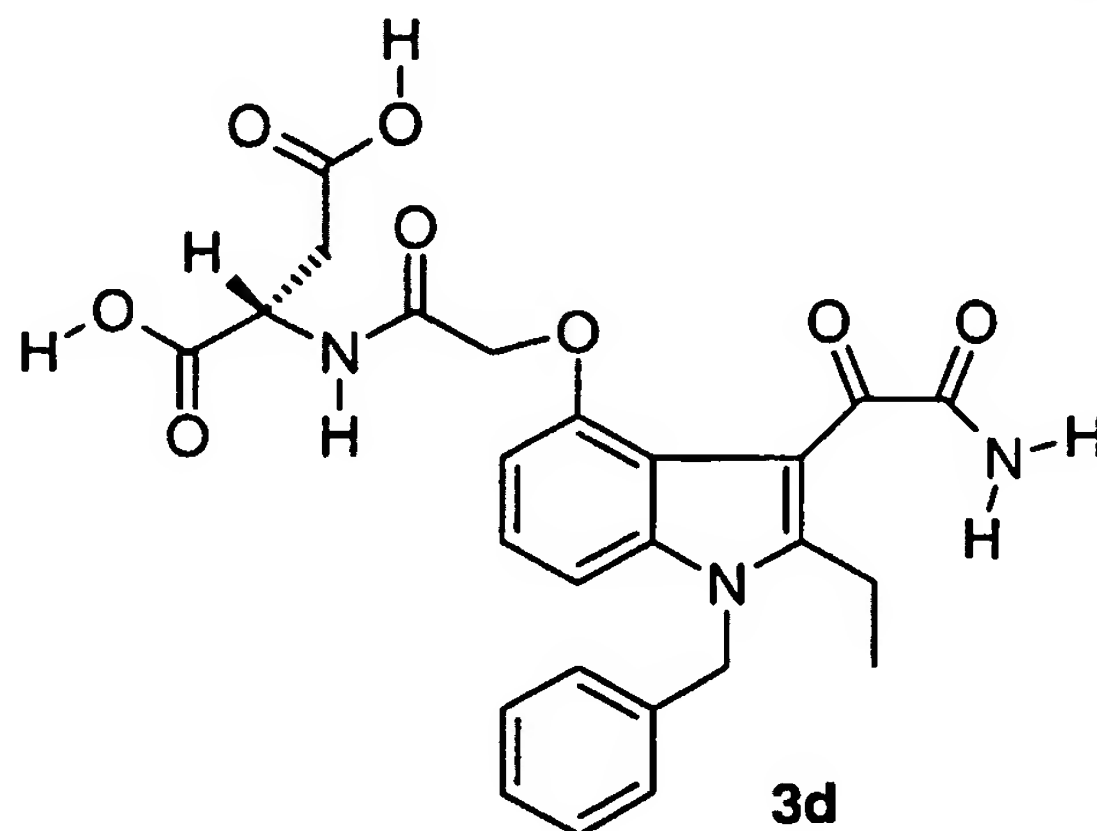


5

Following the experimental procedure as described for 2a, 2d was obtained as a yellow solid in 88% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.3 Hz, 3H), 2.72 (dd, J = 16.6, 7.1 Hz, 1H), 2.83 (dd, J = 16.7, 7.1 Hz, 1H), 2.90 (br q, J = 7.3 Hz, 2H), 3.49 (s, 3H), 3.55 (s, 3H), 4.54 (s, 2H), 4.66 (m, 1H), 5.51 (s, 2H), 6.54 (m, 1H), 6.97-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.50 (s, 1H), 7.97 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H).

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B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid



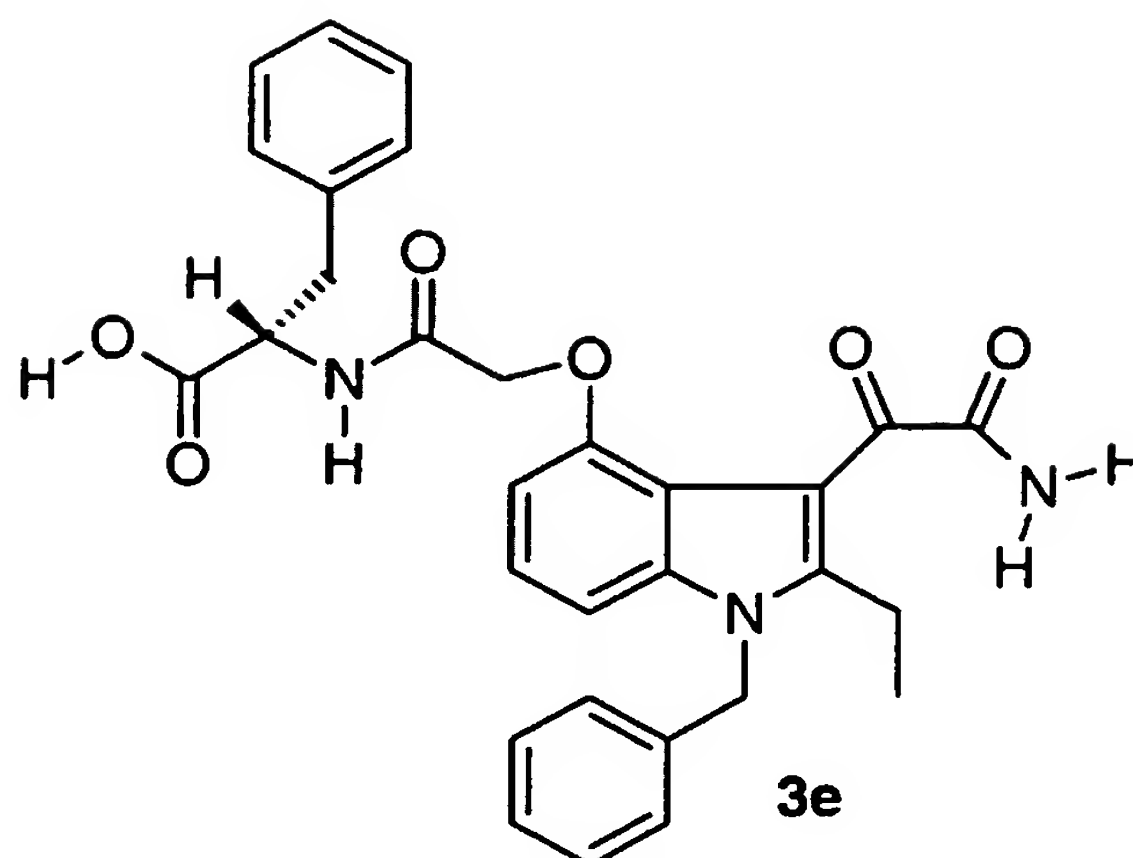
5

Following the experimental procedure as described for 3a, 3d was obtained as a yellow solid in 99% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, *J* = 7.2 Hz, 3H), 2.52-2.76 (m, 2H), 2.90 (br q, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 4.53-4.60 (m, 1H), 5.50 (s, 2H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.19-7.30 (m, 3H), 7.47 (s, 1H), 7.94 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 12.40-13.20 (br s, 2H).

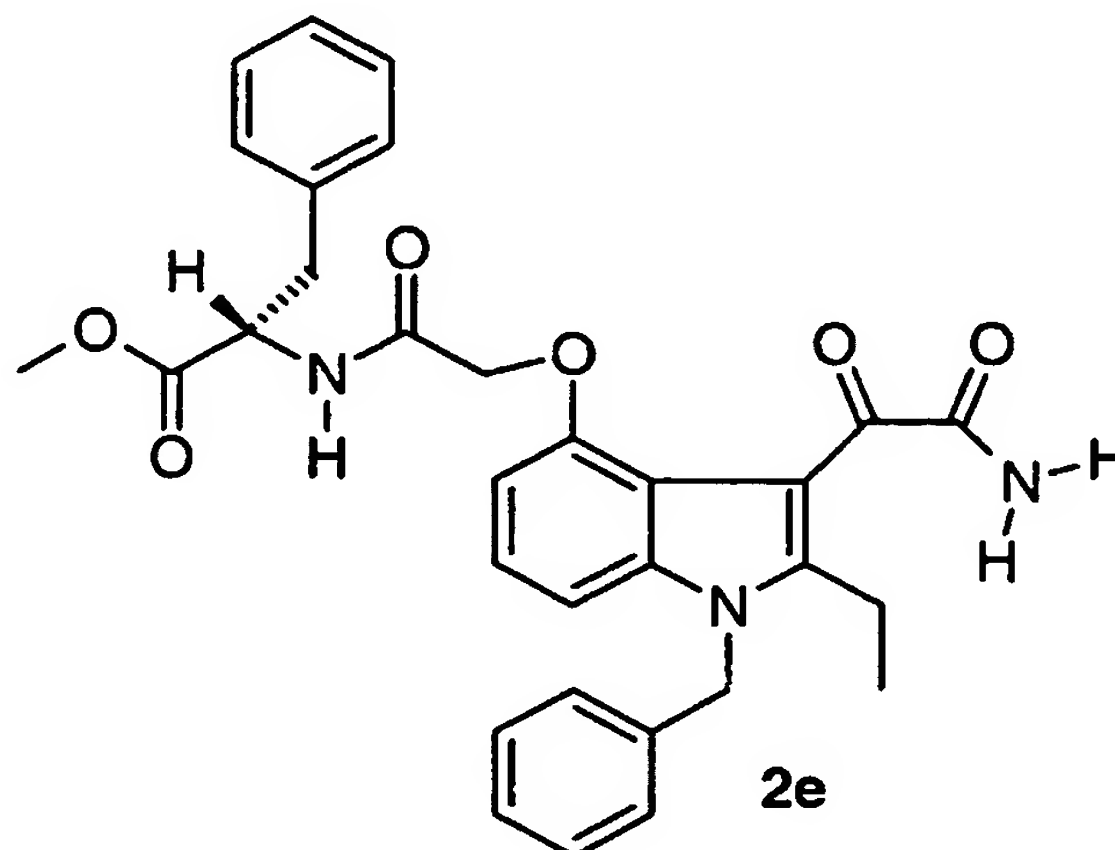
Example 7

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine**

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A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester

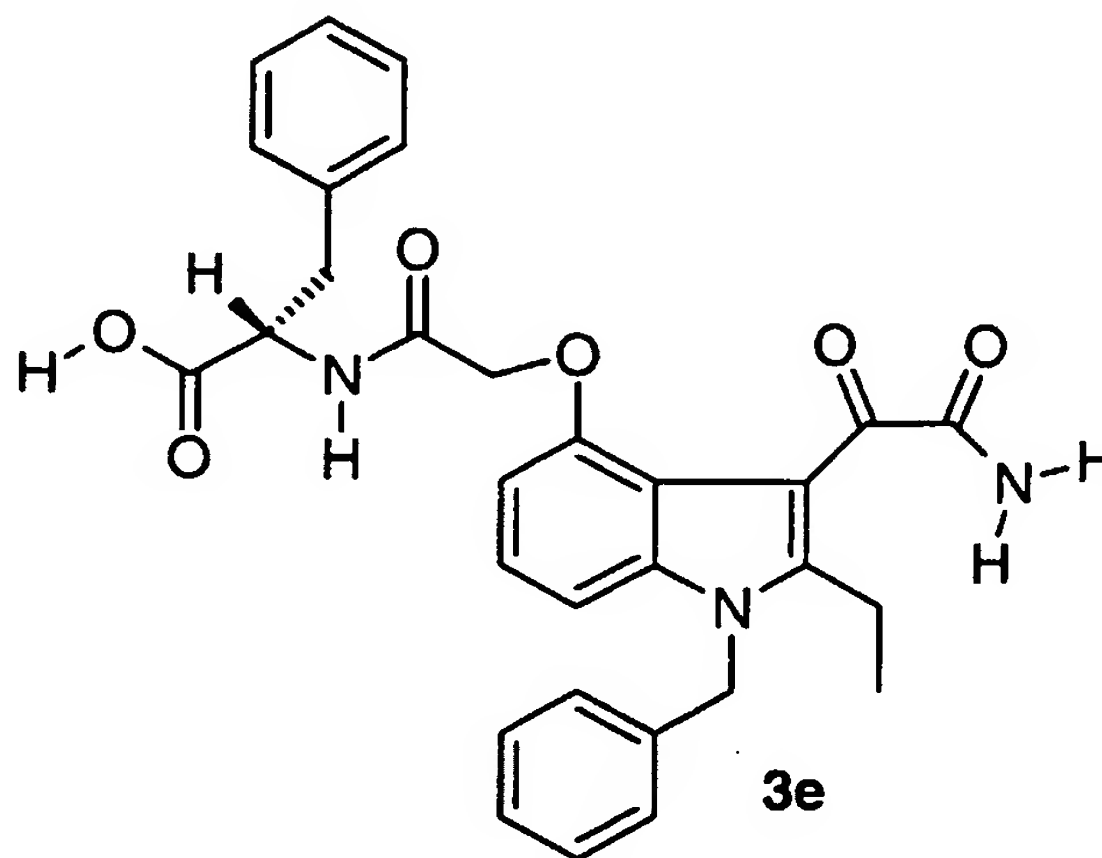


5

Following the experimental procedure as described for 2a, 2e was obtained as a yellow solid in 68% yield. ¹H NMR (DMSO-d₆) δ 1.06 (t, J = 7.2 Hz, 3H), 2.88-3.03 (m, 4H), 3.54 (s, 3H), 4.47-4.50 (m, 1H), 4.50 (s, 2H), 5.52 (s, 2H), 6.41 (d, J = 7.7 Hz, 1H), 6.98-7.11 (m, 9H), 7.21-7.30 (m, 3H), 7.47 (s, 1H), 8.06 (s, 1H), 8.52 (d, J = 7.7 Hz, 1H).

-99-

B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine



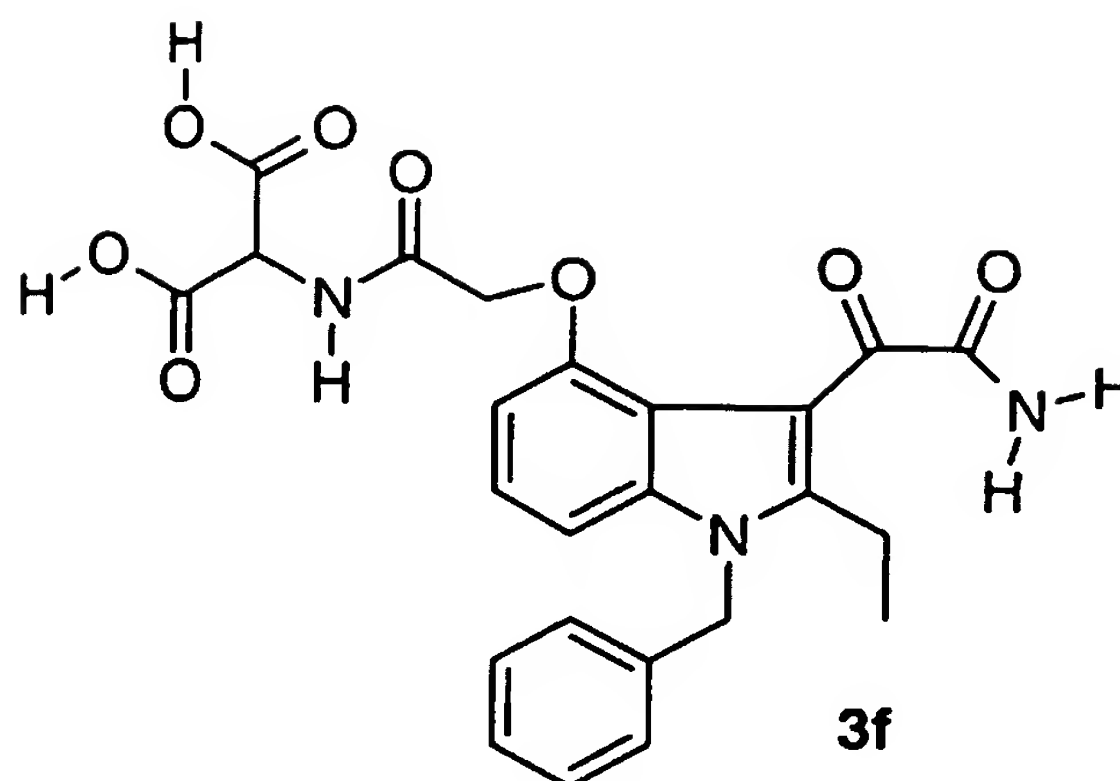
5

Following the experimental procedure as described for 3a, 3e was obtained as a yellow solid in 93% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.1 Hz, 3H), 2.85-3.12 (m, 4H), 4.17-4.26 (m, 1H), 4.54 (s, 2H), 5.51 (s, 2H), 6.59 (d, J = 6.4 Hz, 1H), 6.98-7.09 (m, 9H), 7.19-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.30 (d, J = 7.0 Hz, 1H), 12.50 (br s, 1H).

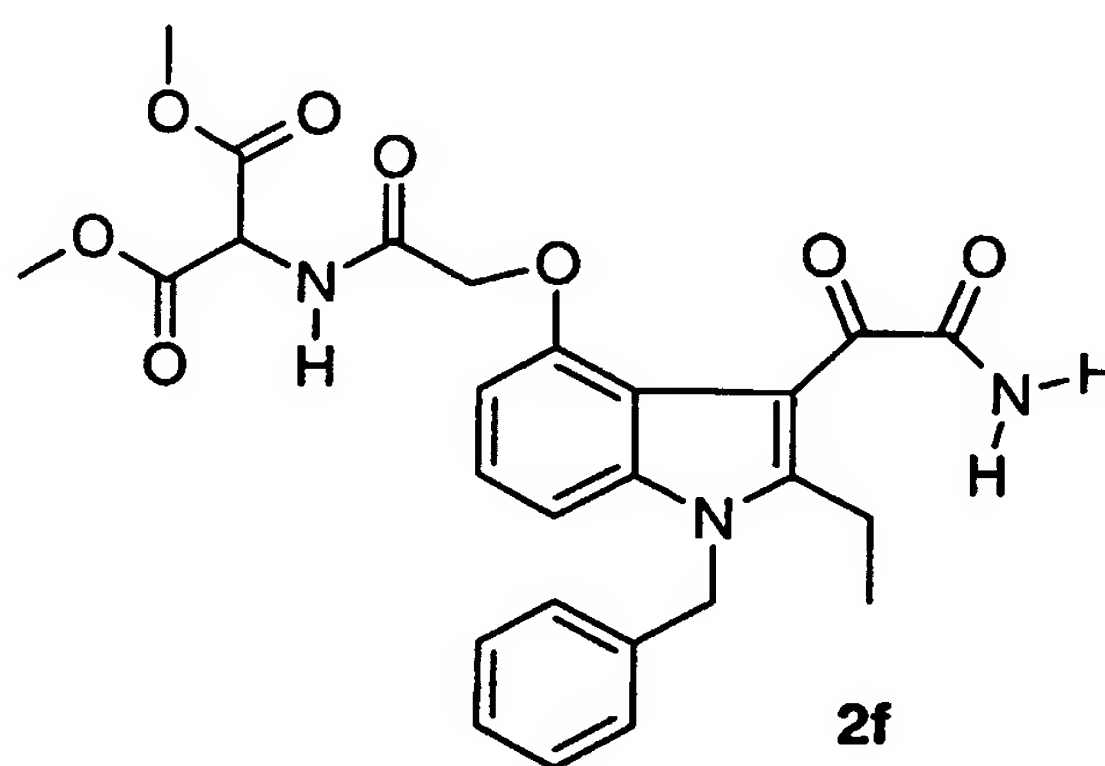
Example 8

15 **[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid**

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A. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester



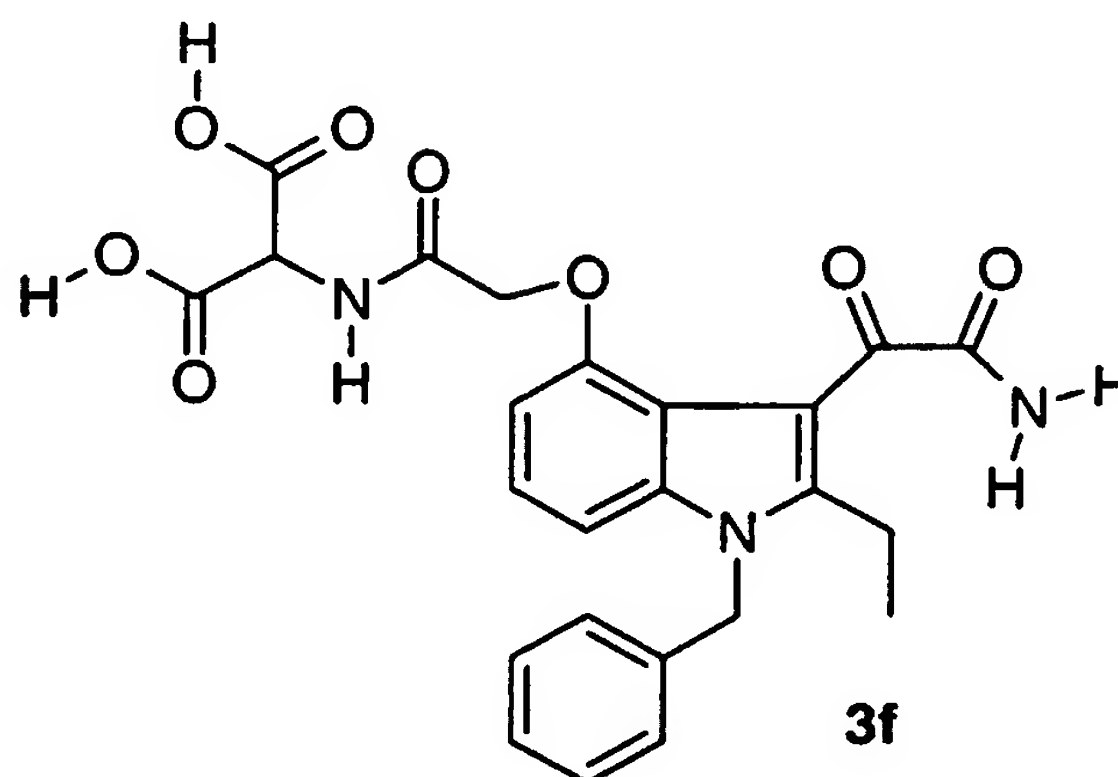
5

Following the experimental procedure as described for 2a, 2f was obtained as a yellow solid in 98% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, *J* = 7.3 Hz, 3H), 2.90 (br q, *J* = 7.3 Hz, 2H), 3.64 (s, 6H), 4.63 (s, 2H), 5.16 (d, *J* = 7.1 Hz, 1H), 5.51 (s, 2H), 6.54-6.56 (m, 1H), 6.98-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.43 (s, 1H), 7.88 (s, 1H), 8.90 (d, *J* = 7.2 Hz, 1H).

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B. Preparation of [2-[[3-(Aminooxoac tyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid

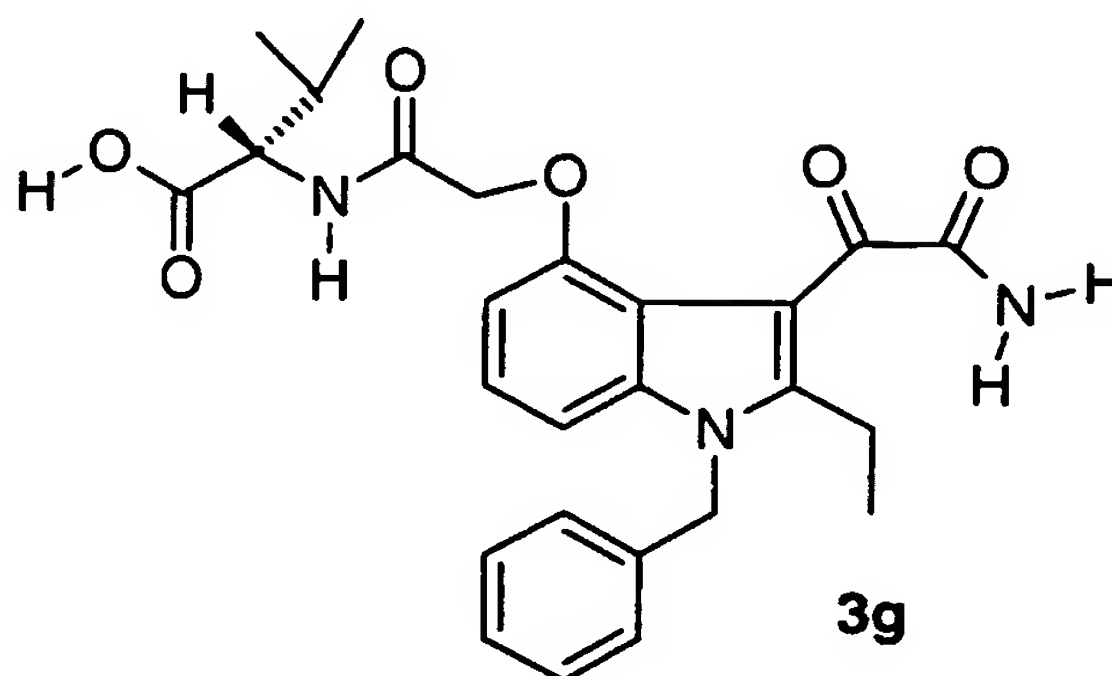


Following the experimental procedure as described for 3a,
5 3f was obtained as a yellow solid in 99% yield. ¹H NMR
(DMSO-d₆) δ 1.04 (t, J = 6.9 Hz, 3H), 2.89 (br q, J = 7.3
Hz, 2H), 4.62 (s, 2H), 4.91 (d, J = 7.2 Hz, 1H), 5.50 (s,
2H), 6.57 (d, J = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.18-
7.30 (m, 3H), 7.37 (s, 1H), 7.83 (s, 1H), 8.55 (d, J = 7.2
10 Hz, 1H), 12.30-13.00 (br s, 2H).

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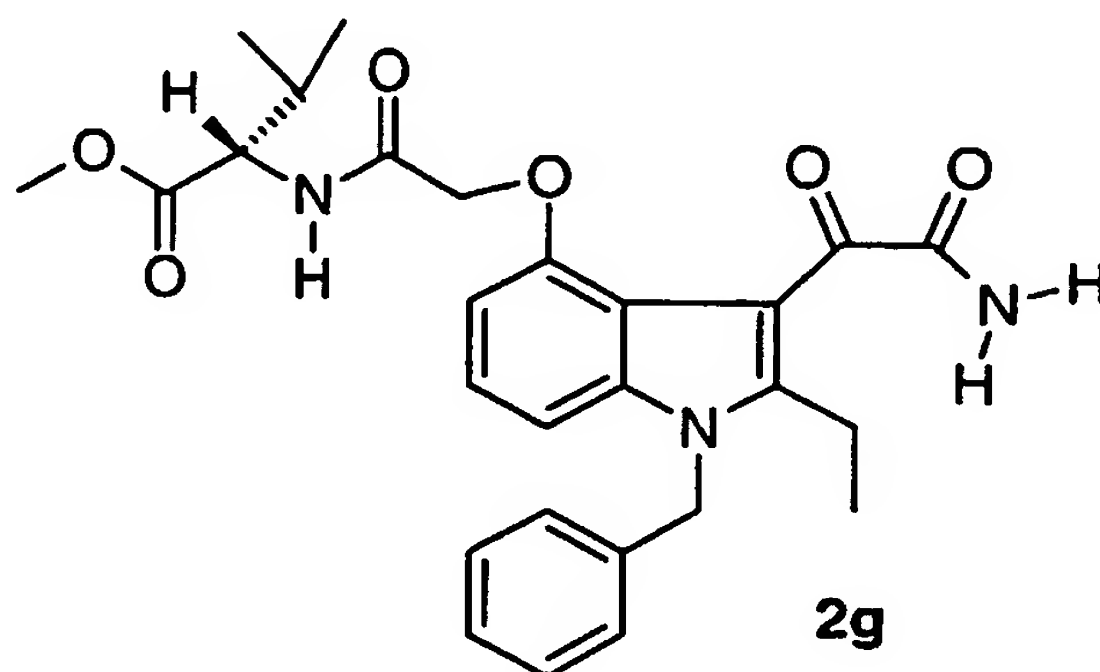
Example 9

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine**



5

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester

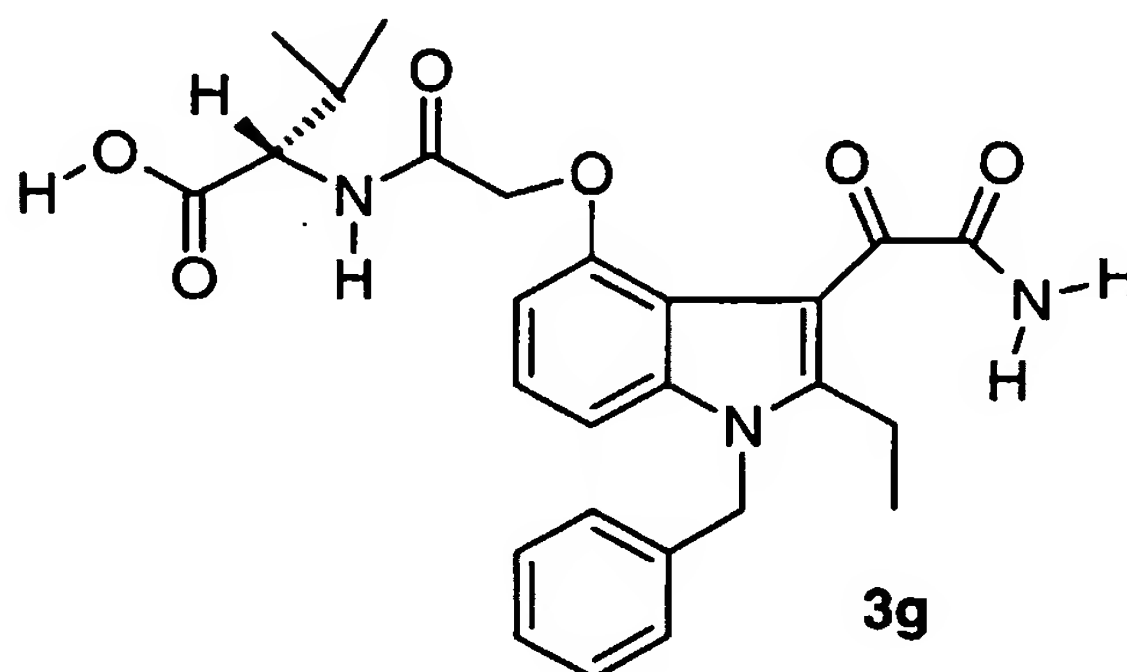


10 Following the experimental procedure as described for 2a,
2g was obtained as a yellow solid in 96% yield. ¹H NMR
(DMSO-d₆) δ 0.71 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 7.0 Hz,
3H), 1.05 (t, *J* = 7.2 Hz 3H), 1.99-2.05 (m, 1H), 2.90 (br
q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 4.11 (br t, *J* = 7.0 Hz,
15 1H), 4.60 (s, 2H), 5.52 (s, 2H), 6.52 (d, *J* = 4.4 Hz, 1H),

-103-

6.95 (d, $J = 7.2$ Hz, 2H), 7.06 (br s, 2H), 7.18-7.29 (m, 3H), 7.52 (s, 1H), 8.04 (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H).

B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine

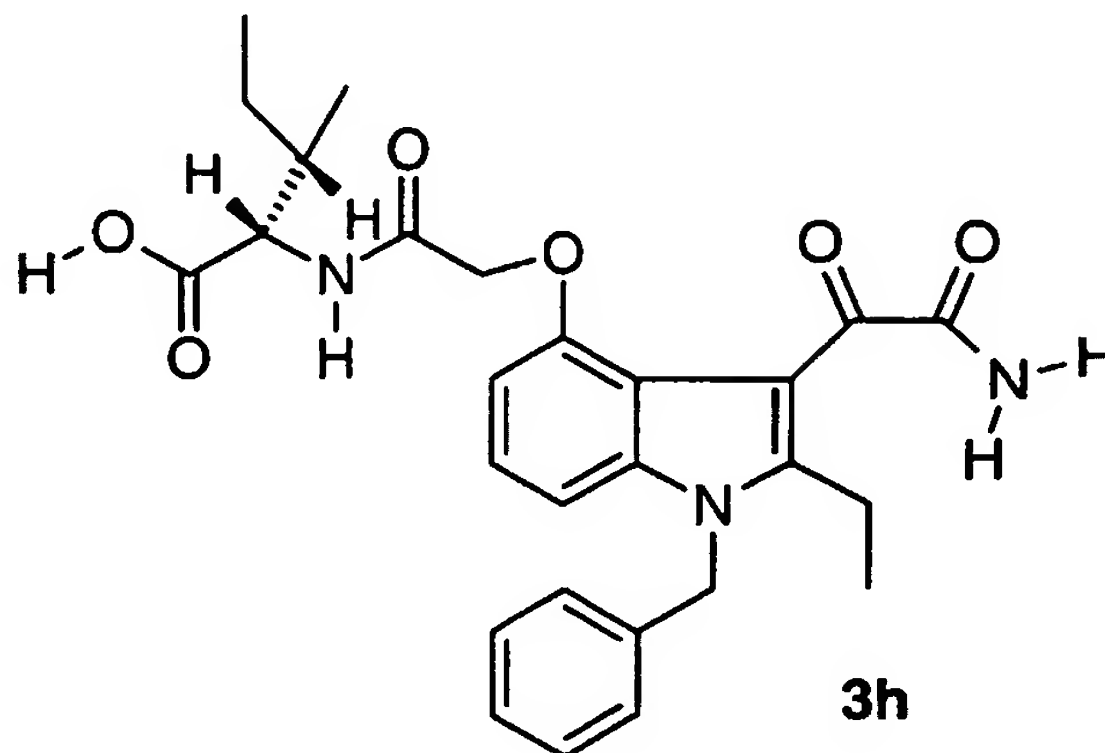


Following the experimental procedure as described for 3a, 3g was obtained as a yellow solid in 94% yield. ^1H NMR (DMSO- d_6) δ 0.71 (d, $J = 6.9$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H), 2.01-2.07 (m, 1H), 2.90 (br q, $J = 7.3$ Hz, 2H), 4.09 (br dd, $J = 7.9, 6.2$ Hz, 1H), 4.60 (s, 2H), 5.51 (s, 2H), 6.54 (d, $J = 6.1$ Hz, 1H), 6.95 (d, $J = 7.3$ Hz, 2H), 6.99-7.08 (m, 2H), 7.18-7.29 (m, 3H), 7.49 (s, 1H), 8.01 (s, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 12.63 (br s, 1H).

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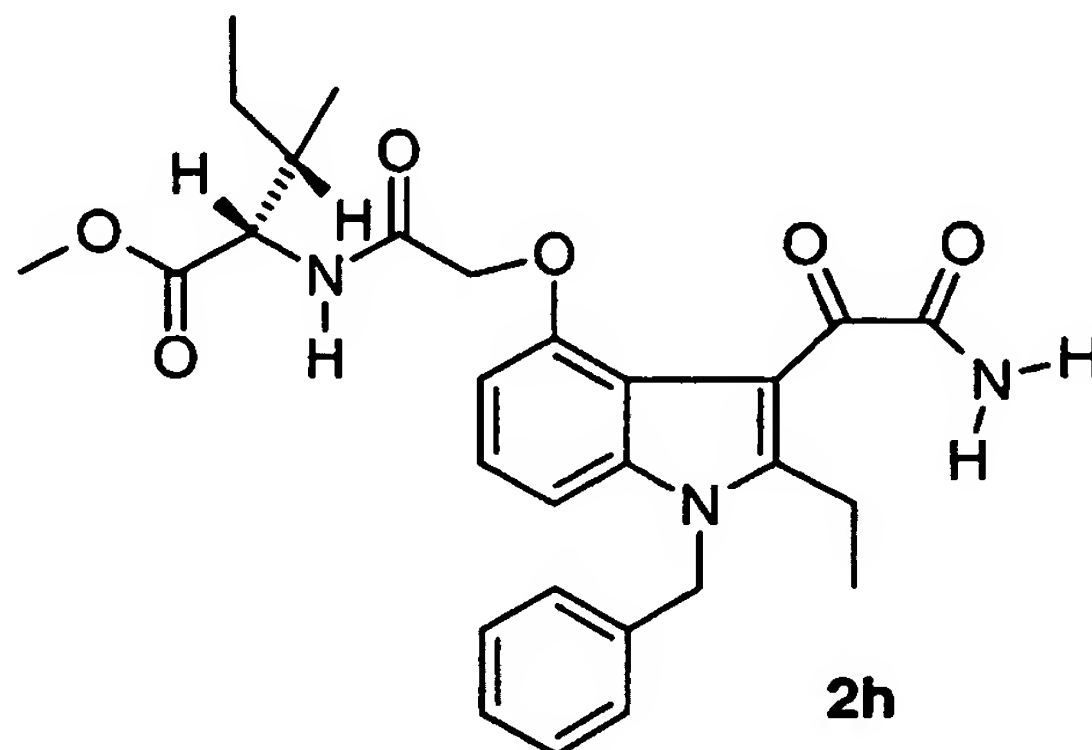
Example 10

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-isoleucine**



5

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-isoleucine methyl ester

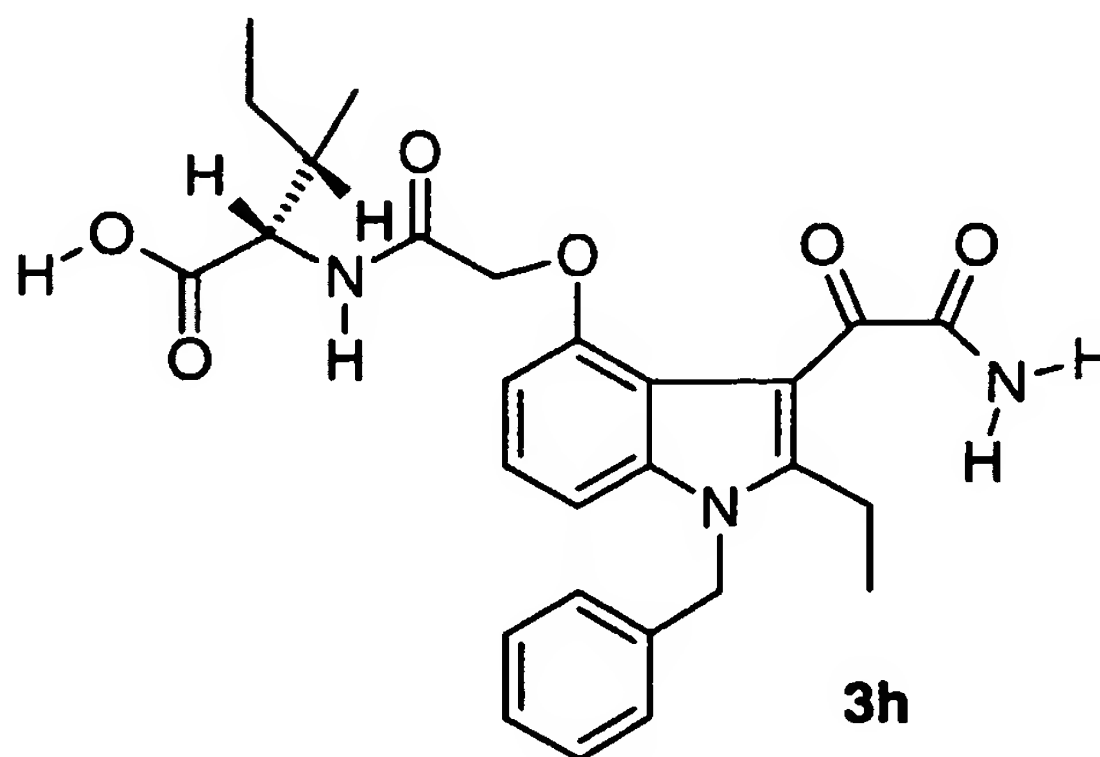


10 Following the experimental procedure as described for 2a, 2h was obtained as a yellow solid in 73% yield. ¹H NMR (DMSO-d₆) δ 0.64-0.71 (m, 6H), 0.99-1.08 (m, 4H), 1.21-1.26 (m, 1H), 1.76-1.80 (m, 1H), 2.91 (br q, *J* = 7.4 Hz, 2H), 3.53 (s, 3H), 4.15 (br t, *J* = 7.2 Hz, 1H), 4.60 (s,

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2H), 5.52 (s, 2H), 6.52 (m, 1H), 6.96 (d, $J = 7.2$ Hz, 2H), 7.02-7.07 (m, 2H), 7.18-7.29 (m, 3H), 7.53 (s, 1H), 8.04 (s, 1H), 8.23 (d, $J = 7.7$ Hz, 1H).

5 **B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine**



Following the experimental procedure as described for 3a,
10 3h was obtained as a yellow solid in 92% yield. ^1H NMR
(DMSO- d_6) δ 0.64-0.84 (m, 6H), 1.04 (t, $J = 7.2$ Hz, 3H),
1.21-1.28 (m, 2H), 1.76-1.80 (m, 1H), 2.91 (br q, $J = 7.2$
Hz, 2H), 4.12 (br t, $J = 7.3$ Hz, 1H), 4.59 (s, 2H), 5.51
(s, 2H), 6.55 (d, $J = 6.4$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz,
15 2H), 7.01-7.08 (m, 2H), 7.21-7.29 (m, 3H), 7.51 (s, 1H),
8.01 (s, 1H), 8.11 (d, $J = 7.4$ Hz, 1H), 12.40-12.65 (br s,
1H).

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Assay

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A₂. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A₂ on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

15 Reagents:

REACTION BUFFER -

CaCl₂·2H₂O (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)

20 (Sigma A-7030, product of Sigma
Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

25 0.05 NaOAc·3H₂O, pH 4.5

0.2 NaCl

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Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

5 racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-glycero-3-phosphorylcholine

TRITON X-100™ prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

10 A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

TRITON X-100™ nonionic detergent aqueous solution.

15 Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mM Triton X-100™ detergent, and 0.12 mM DTMB in a buffered aqueous solution at pH 7.5.

20

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
- 25 3. Add 50 nanograms of sPLA₂ (10 microliters) to appropriate wells;

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4. Incubate plate at 40 °C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

5 All compounds were tested in triplicate.

Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured

10 at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC₅₀ values were determined. Typically, the IC₅₀ values (see, Table I,

15 below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405

20 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC₅₀ values. IC₅₀ were determined by

25 plotting log concentration versus inhibition values in the range from 10-90% inhibition.

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Results of Human Secreted Phospholipase A₂ Inhibition
Tests

Table

Compound No. from Examples 3-10	Inhibition of human secreted PLA ₂ IC ₅₀ ± mean deviation (3-4 tests) (nM)
1	49
2A	529
2B	533
2C	82
2D	874
2E	666
2F	698
2G	283
2H	166
3A	71
3B	59
3C	28
3D	132
3E	64
3F	44.7
3G	36.4
3H	25.1

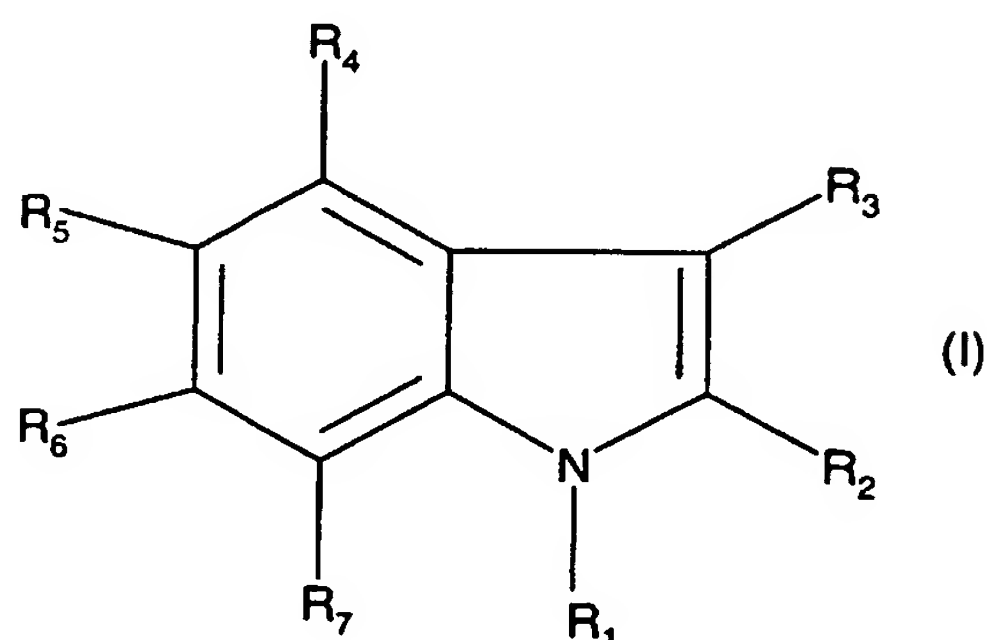
5 The compound of Example 1 is highly active in
inhibiting sPLA₂.

While the present invention has been illustrated
above by certain specific embodiments, it is not intended
10 that these specific examples should limit the scope of the
invention as described in the appended claims.

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WE CLAIM:

1. An indole compound represented by the formula
(I), or a pharmaceutically acceptable salt, solvate, or
5 prodrug derivative thereof;



wherein ;

- 10 R₁ is selected from groups (a), (b), and (c)

wherein;

(a) is C₇-C₂₀ alkyl, C₇-C₂₀ haloalkyl, C₇-C₂₀ alkenyl, C₇-C₂₀ alkynyl, carbocyclic radical, or heterocyclic radical, or

- 15 (b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

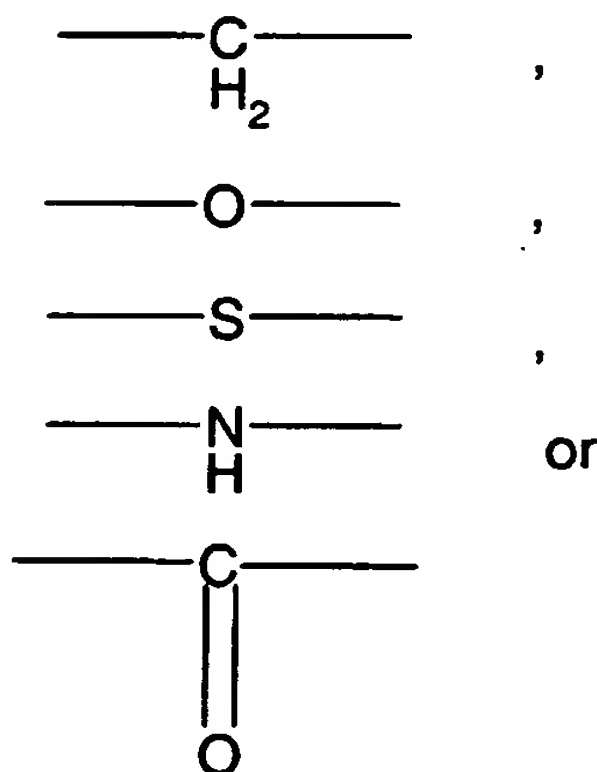
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(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

5 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

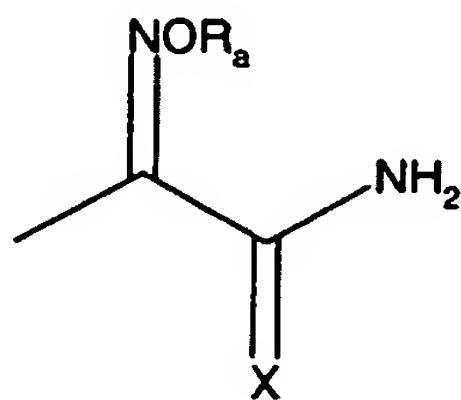
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:

10

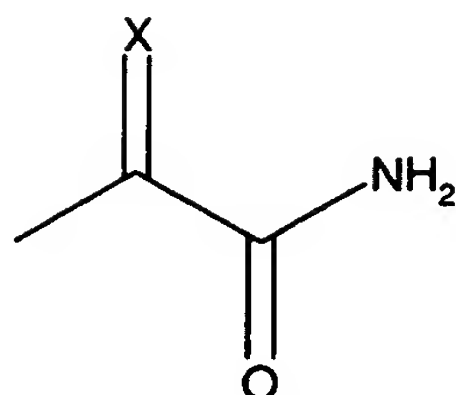


and Z is selected from a group represented by the formulae,

15

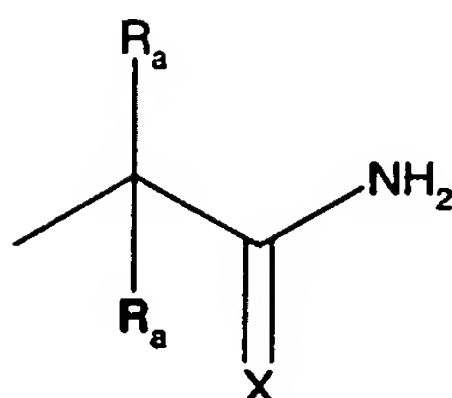


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or

5



wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R_4 is the group, $-(L_c)-(acylamino\ acid\ group)$;

wherein $-(L_c)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein
 15 $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

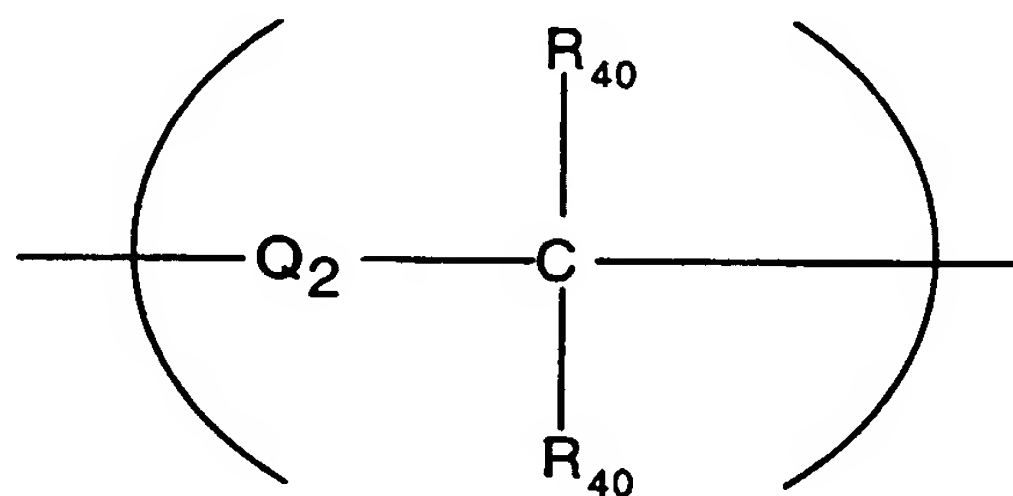
R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),

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heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

2. The compound of claim 1 wherein R_2 is
 5 hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, $-O-(C_1-C_3 \text{ alkyl})$,
 $-S-(C_1-C_3 \text{ alkyl})$, C_3 - C_4 cycloalkyl, $-CF_3$, halo, $-NO_2$, $-CN$, or $-SO_3$.

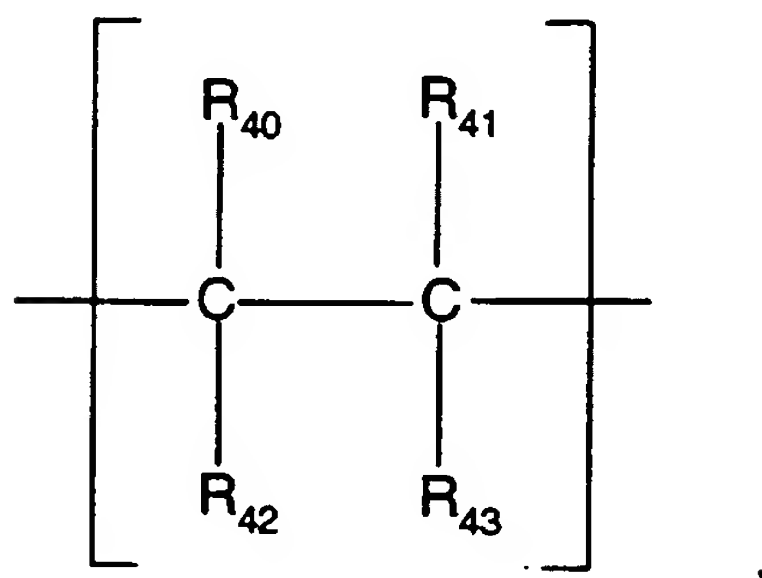
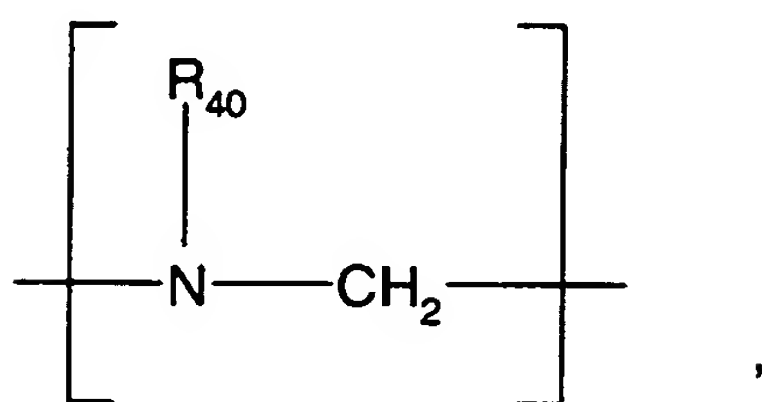
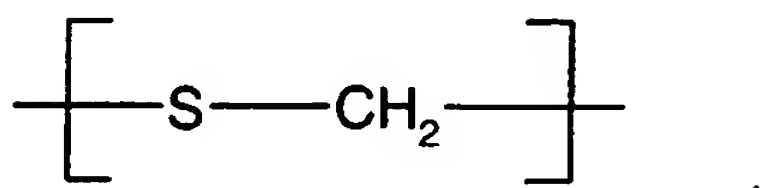
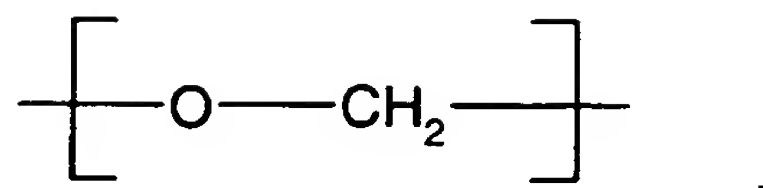
3. The compound of Claim 1 wherein the acylamino
 10 acid linker group, $-(L_C)-$, for R_4 is selected from a
 group represented by the formula;



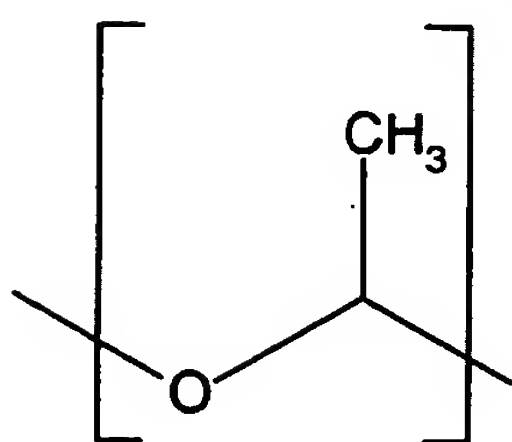
15 where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$,
 $-C(O)-$, and $-S-$, and each R_{40} is independently selected
 from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8
 alkoxy, aralkyl, and halo.

20 4. The compound of Claim 1 wherein the acylamino
 acid linker group, $-(L_C)-$, for R_4 selected from $-(L_C)-$
 is a divalent group selected from,

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or

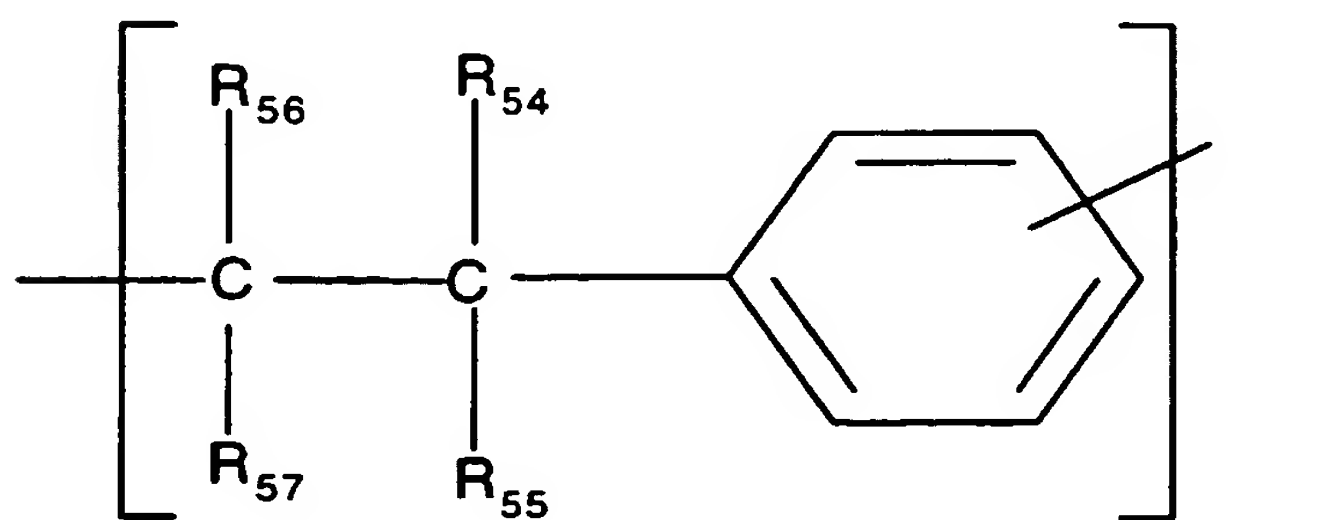
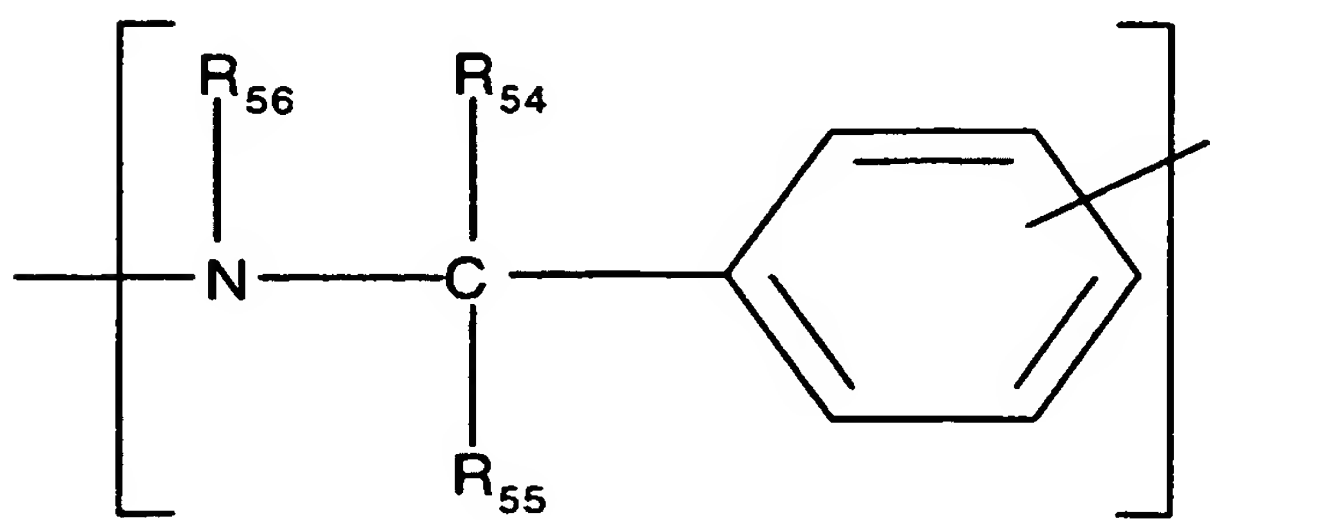
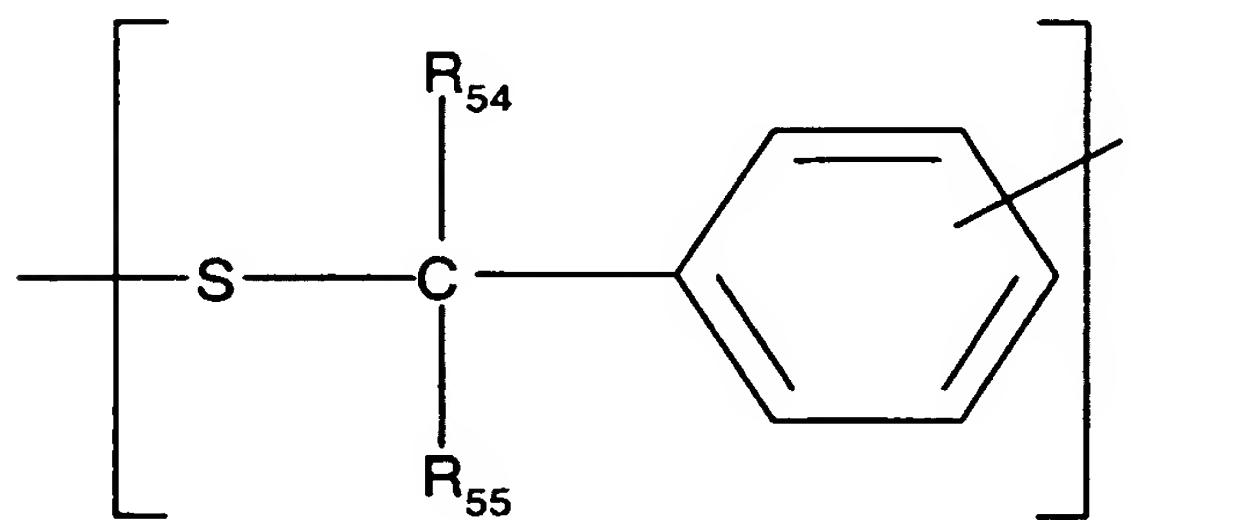
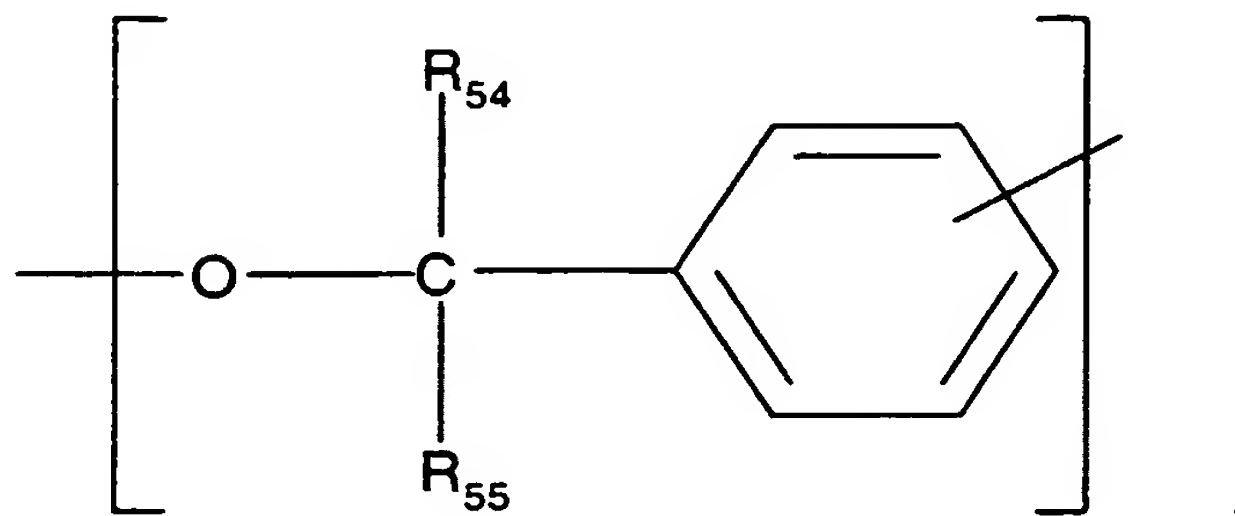


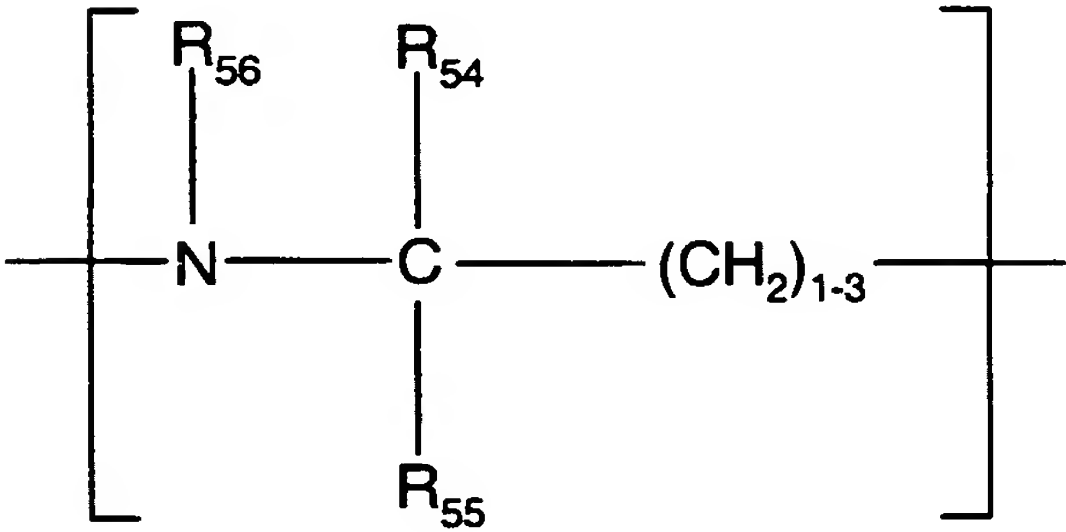
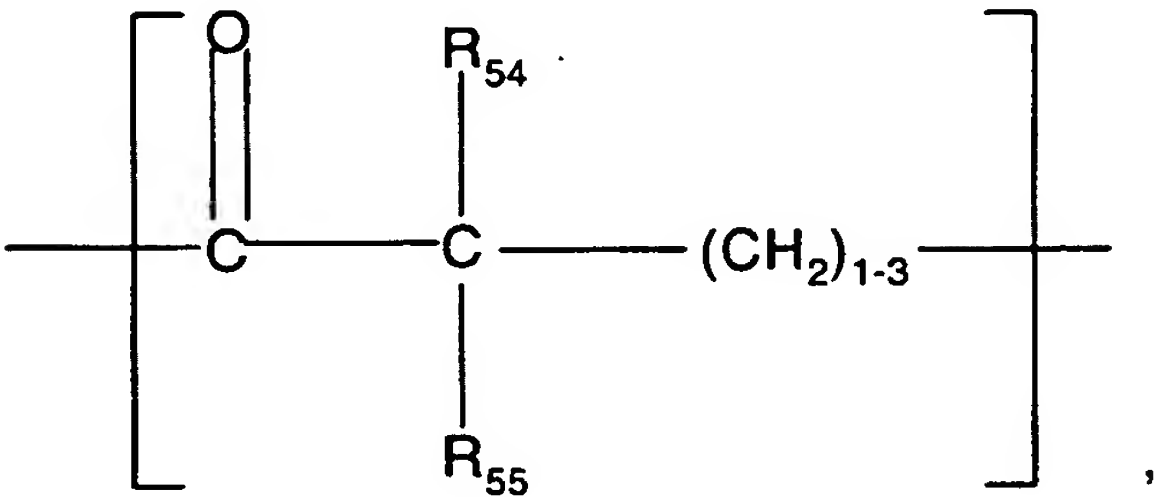
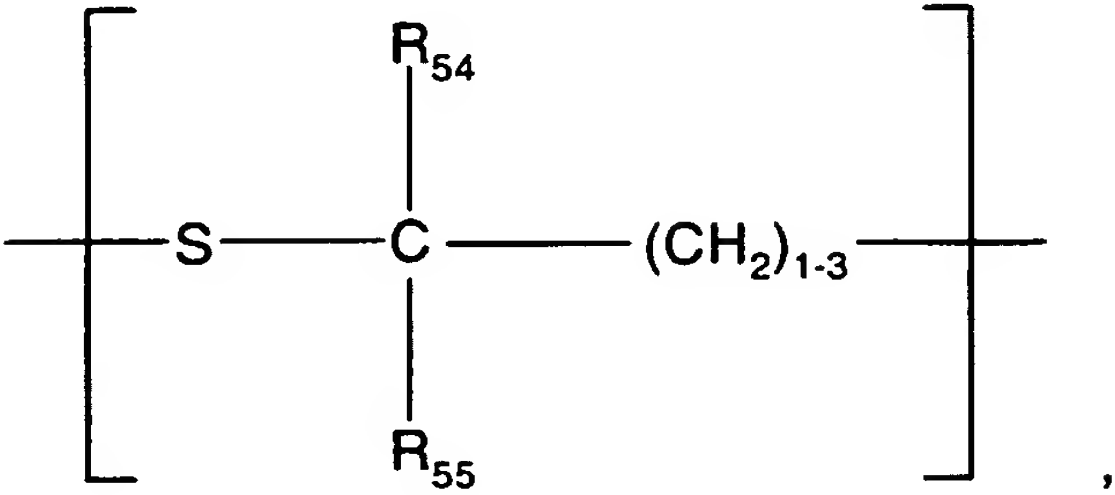
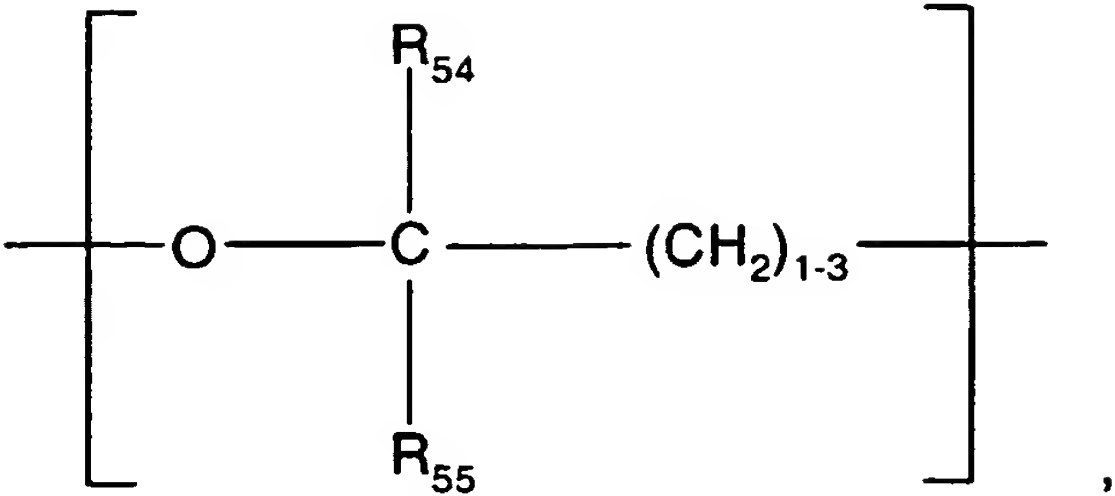
5

where R_{40} , R_{41} , R_{42} , and R_{43} are each independently selected from hydrogen, C_1 - C_8 alkyl.

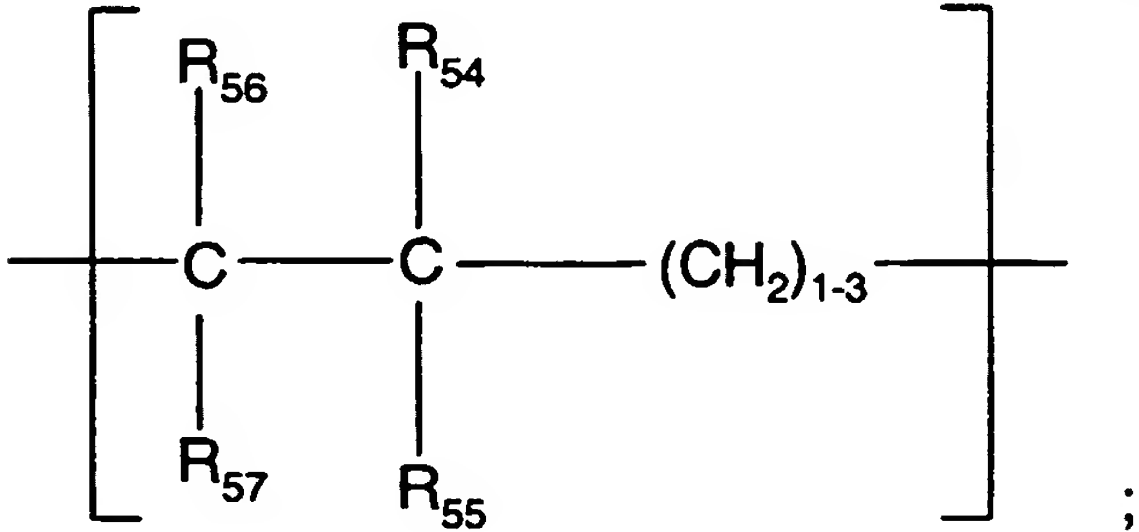
-115-

5. The compound of Claim 1 wherein the acid linker, $-(L_a)-$, for R_5 is selected from a group represented by the formulae consisting of;





and



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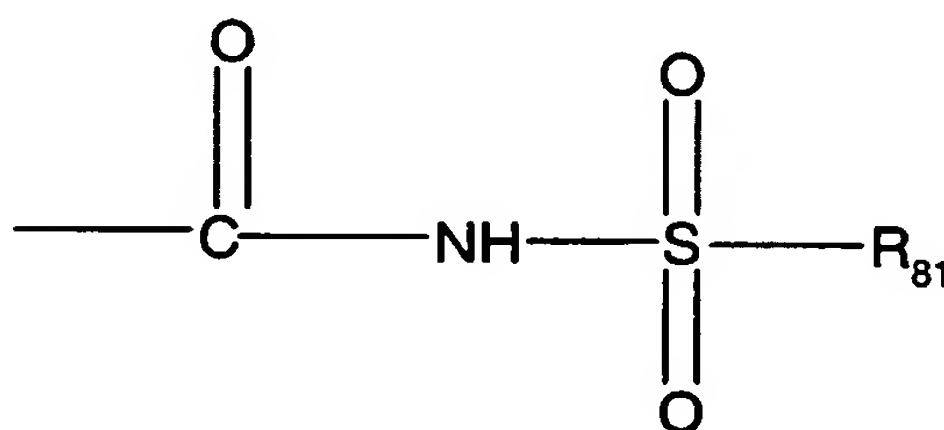
wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo.

- 5 6. The compound of claim 1 wherein R₅ is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

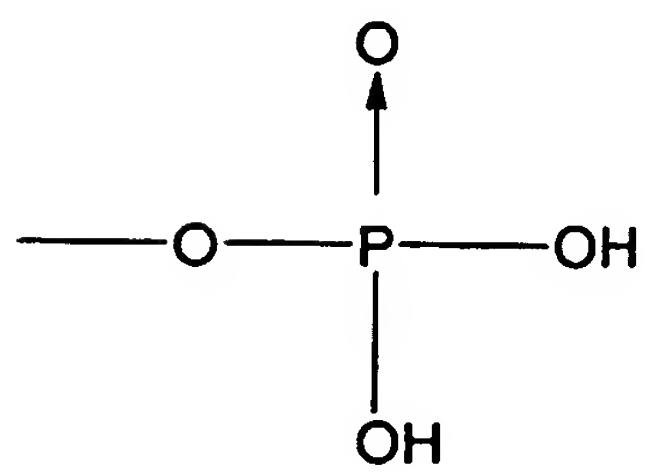
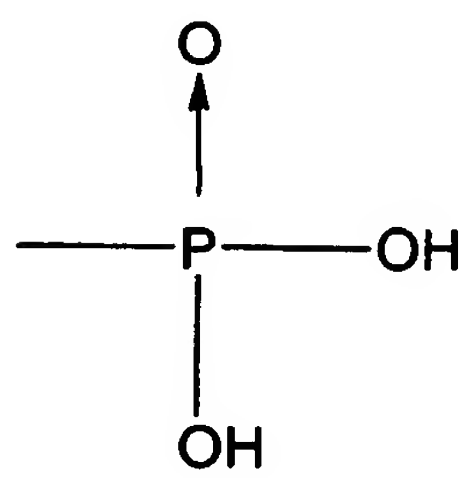
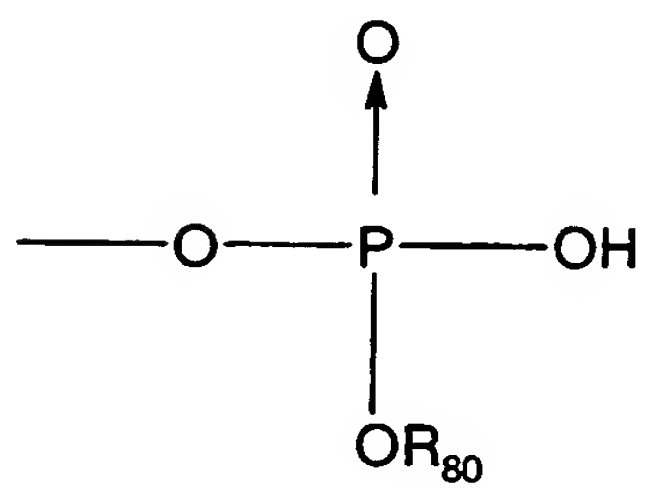
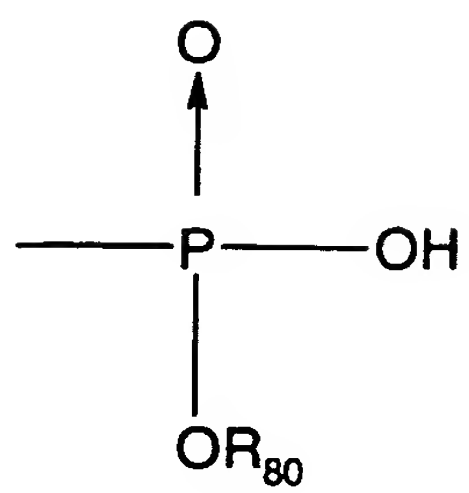
-5-tetrazolyl,

10

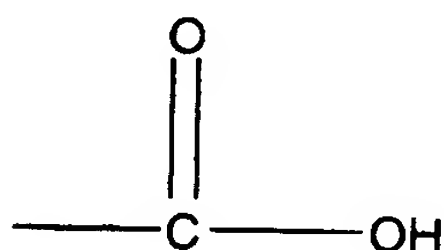
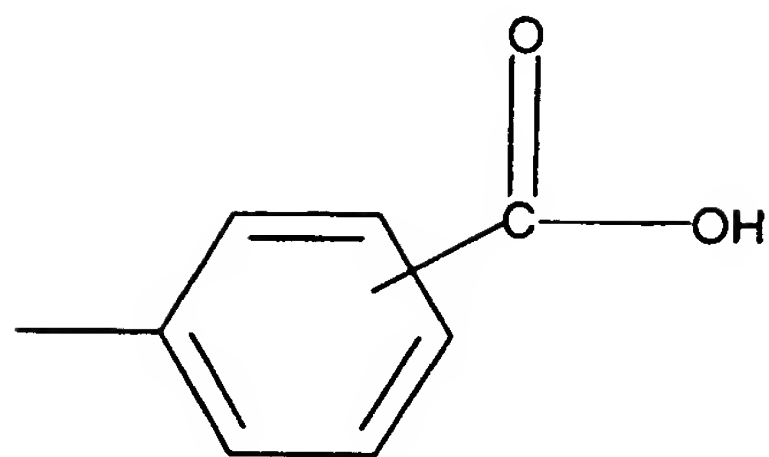
-SO₃H,



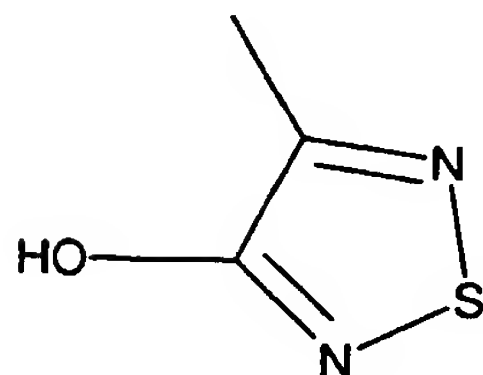
-118-



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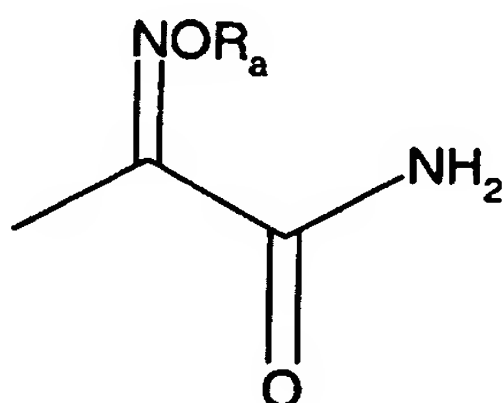


or



where R₈₀ is a metal or C₁-C₈ alkyl and R₈₁ is an organic substituent or -CF₃.

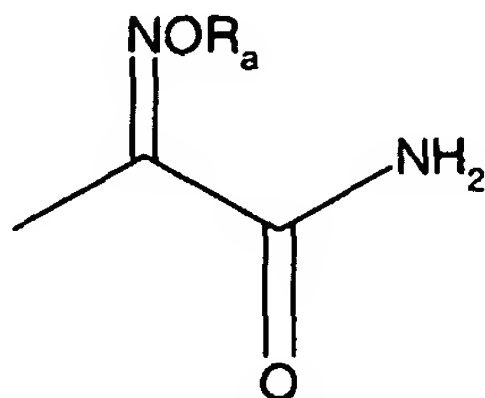
- 5 7. The compound of claim 1 wherein for R₃, Z is the group represented by the formula;



and the linking group -(L₃)- is a bond; and R_a is
 10 hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

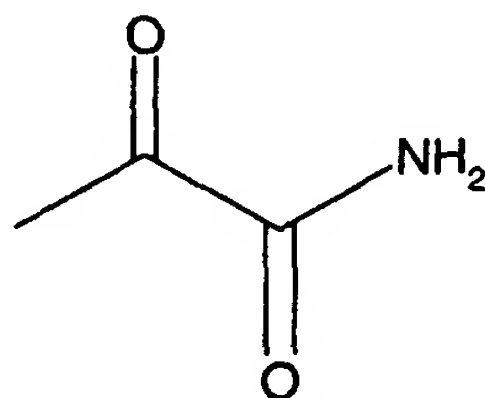
-120-

8. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



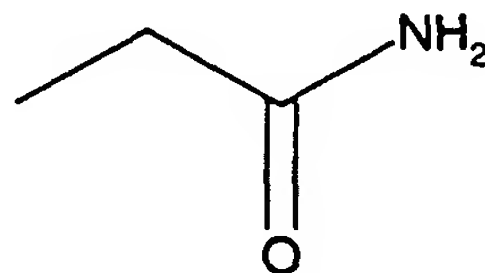
and the linking group $-(L_3)-$ is a bond; and R_a is
5 hydrogen.

9. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



10 and the linking group $-(L_3)-$ is a bond.

10. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



15 and the linking group $-(L_3)-$ is a bond.

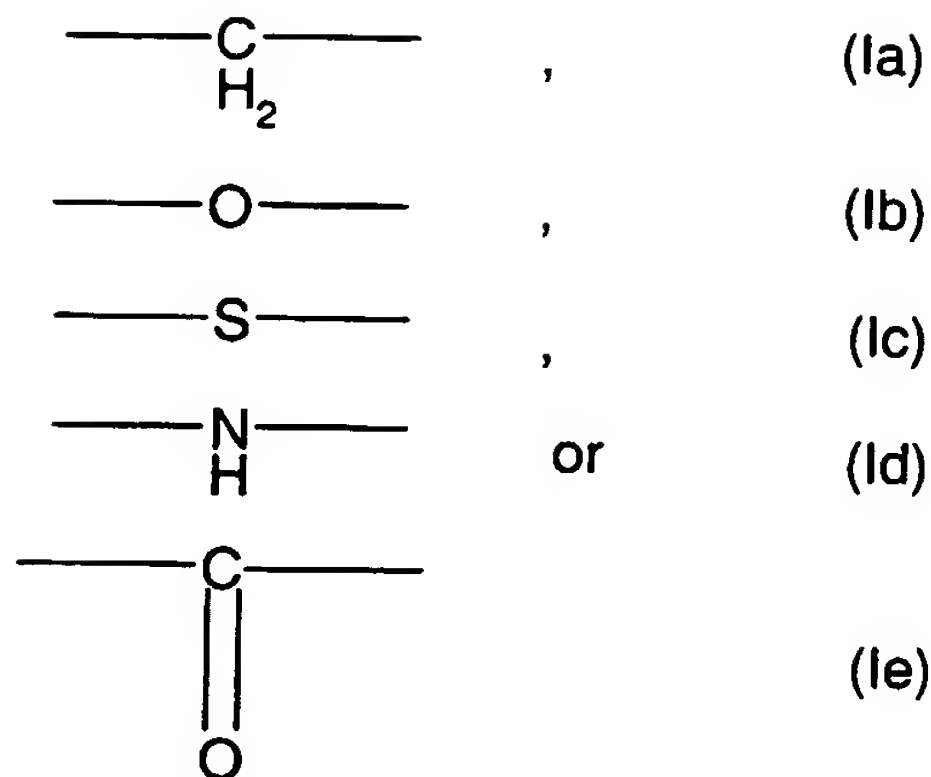
11. The compound of Claim 1 wherein, for R_6 the non-interfering substituent is hydrogen, C₁-C₈ alkyl,

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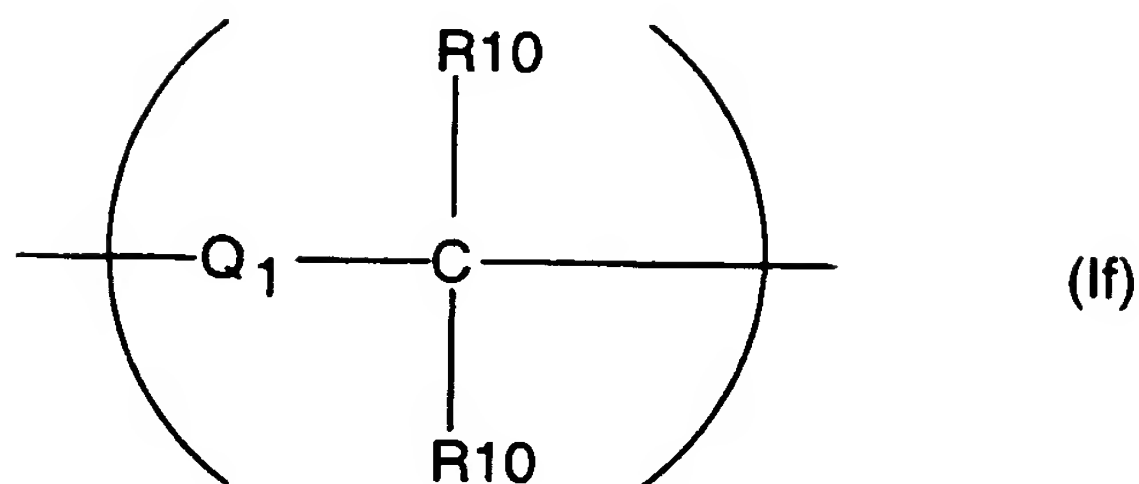
- C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈ alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

12. The compound of Claim 1 wherein for R₁ the divalent linking group -(L₁)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):

-122-



or

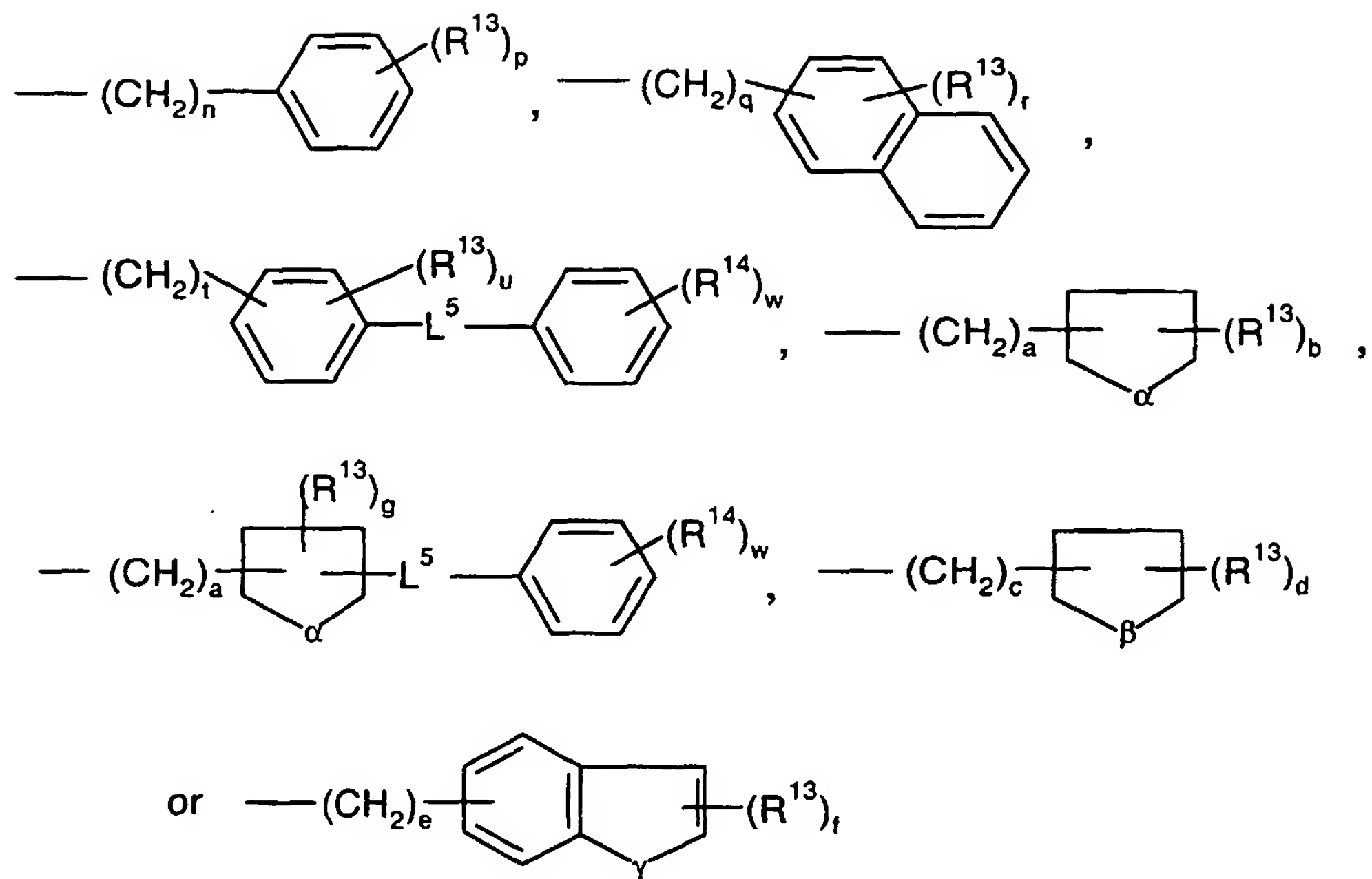


5 where Q₁ is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R₁₀ is independently -H, C₁₋₈ alkyl, C₁₋₈ haloalkyl or C₁₋₈ alkoxy.

13. The compound of claim 1 wherein the linking
 10 group -(L₁)- of R₁ is -(CH₂)- or -(CH₂-CH₂)-.

14. The compound of claim 1 wherein the linking
 group -(L₁₁)- of R₁₁ is a bond and R₁₁ is -(CH₂)_m-R¹²
 wherein m is an integer from 1 to 6, and R¹² is a group
 15 represented by the formula:

-123-

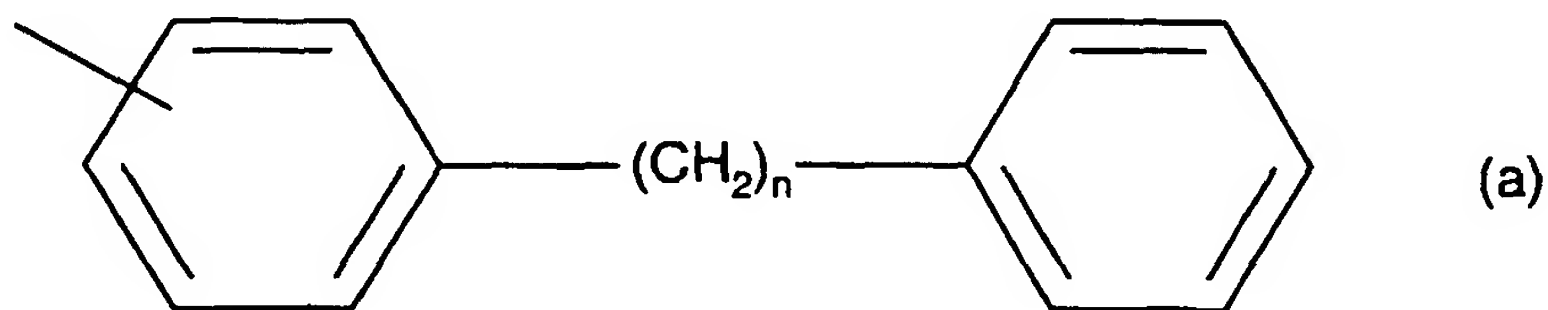


wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$, $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group

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consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen..

15. The compound of claim 1 wherein for R₁ the
5 group R₁₁ is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl,
10 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):

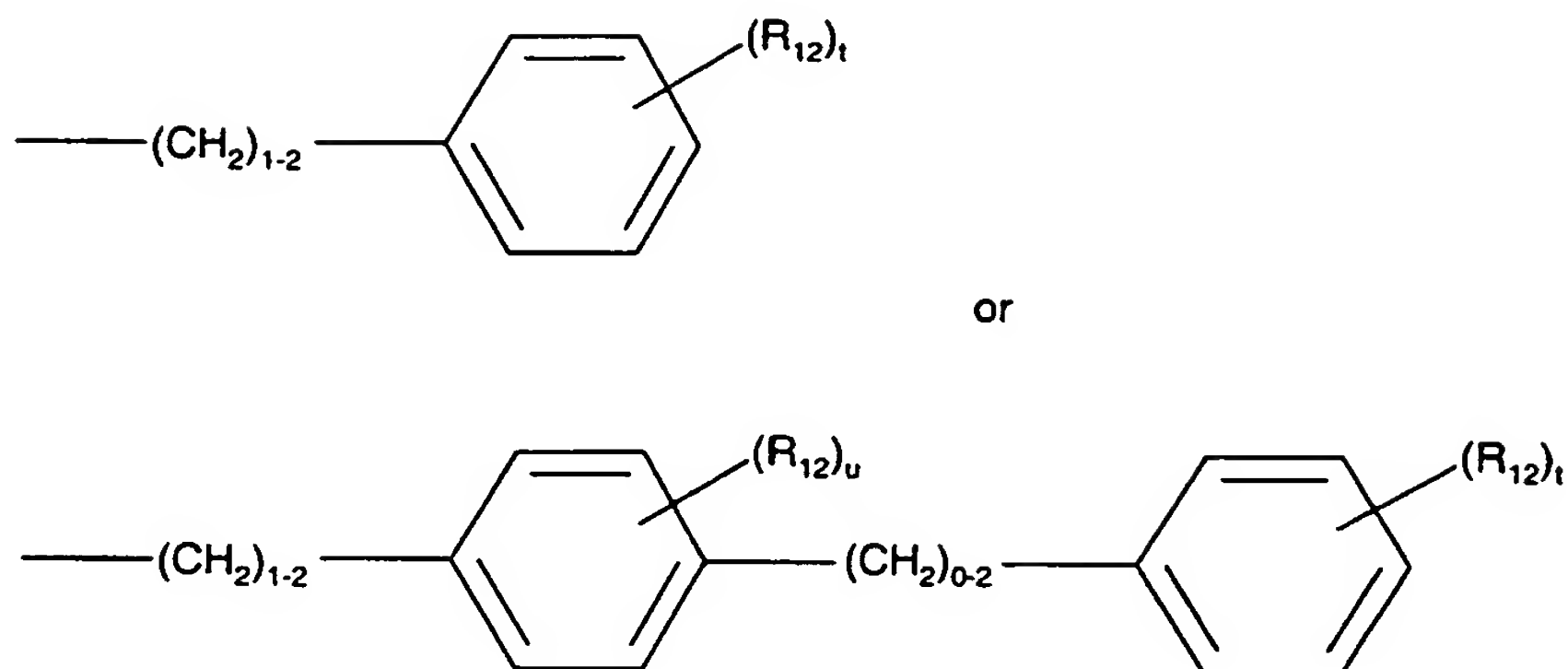


where n is a number from 1 to 8.

15

16. The compound of Claim 12 wherein for R₁ the combined group $-(L_1)-R_{11}$ is selected from the groups;

-125-



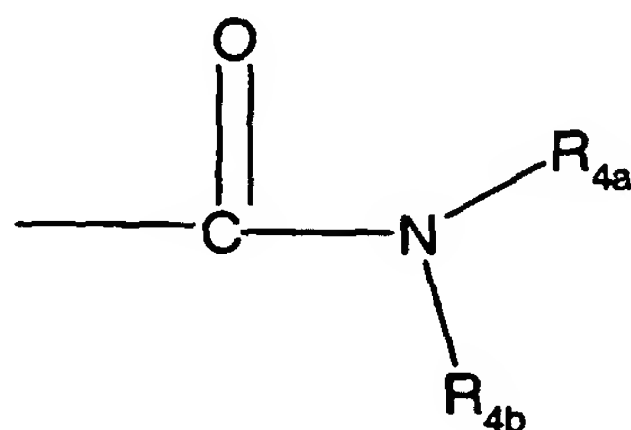
where R_{12} is a radical independently selected from halo, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, $-S-(C_1-C_{10} \text{ alkyl})$, and C_1 - C_{10} haloalkyl, C_1 - C_{10} hydroxyalkyl and t is a number from 0 to 5 and u is a number from 0 to 4.

17. The compound of claim 1 wherein for R_1 the radical R_{11} is a substituted or unsubstituted heterocyclic radical selected from pyrrolyl, pyrrolodinyll, piperidinyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl,

-126-

quinazolinylmorpholino, thiomorpholino, homopiperazinyl,
 tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-
 dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
 tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-
 5 dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny,
 hexamethyleneiminium, heptamethyleneiminium, piperazinyl
 or quinoxaliny.

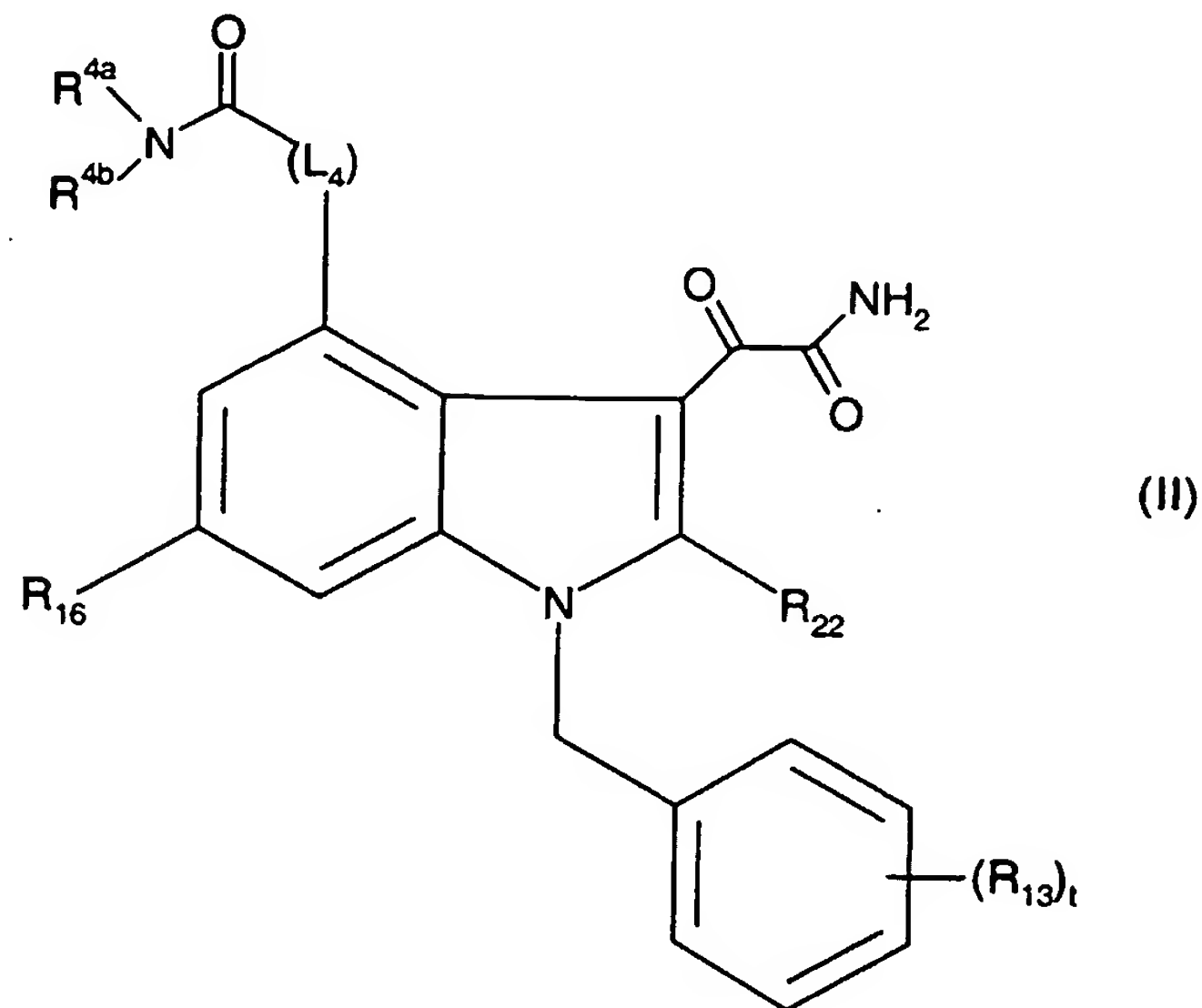
18. The compound of claim 1 wherein R₄ is the
 10 group, -(L_C)-(acylamino acid group) and wherein the
 (acylamino acid group) is:



15 and R^{4a} is selected from the group consisting of H, (C₁-
 C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein
 NR^{4b} is an amino acid residue of a natural or unnatural
 amino acid with the nitrogen atom being part of the amino
 group of the amino acid.

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19. An indole compound represented by the formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof;



5

wherein ;

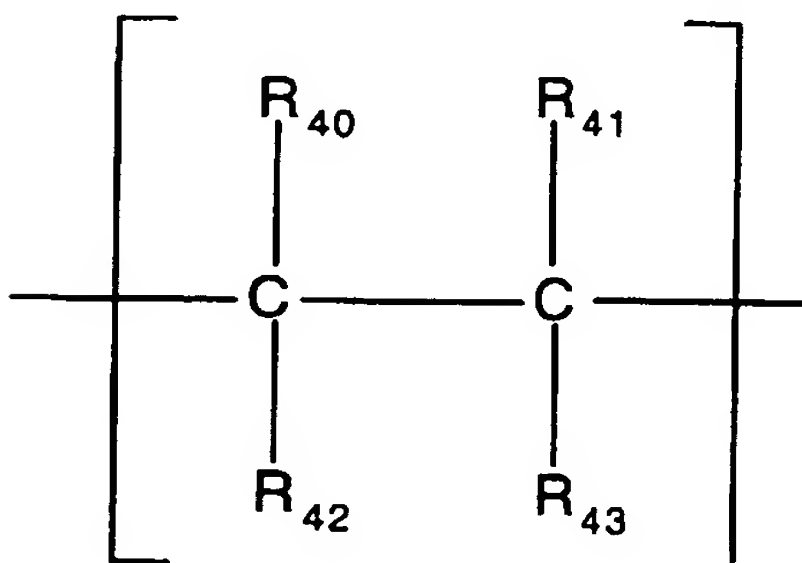
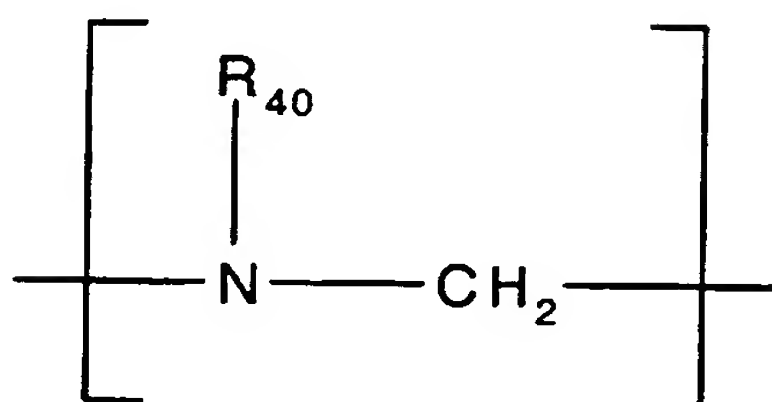
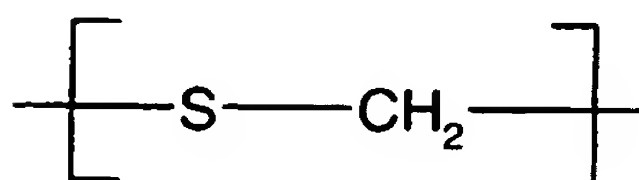
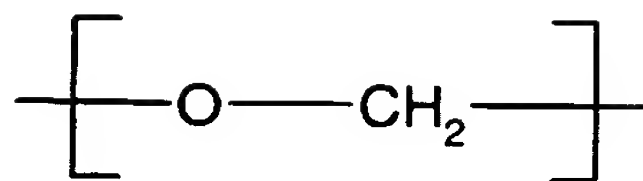
R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃;

R^{4a} is hydrogen; and

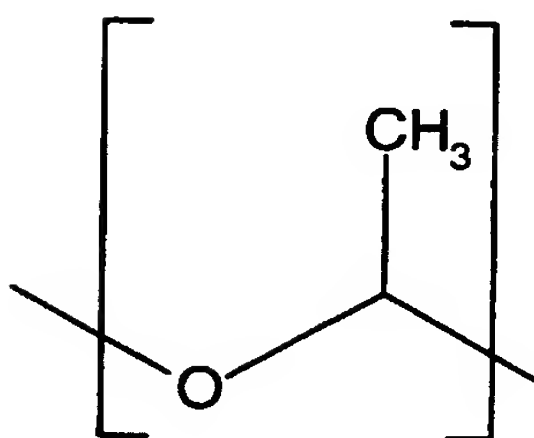
NR^{4b} is an amino acid residue of a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid, and $-(L_C)-$ is a divalent group selected from;

15

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or



5

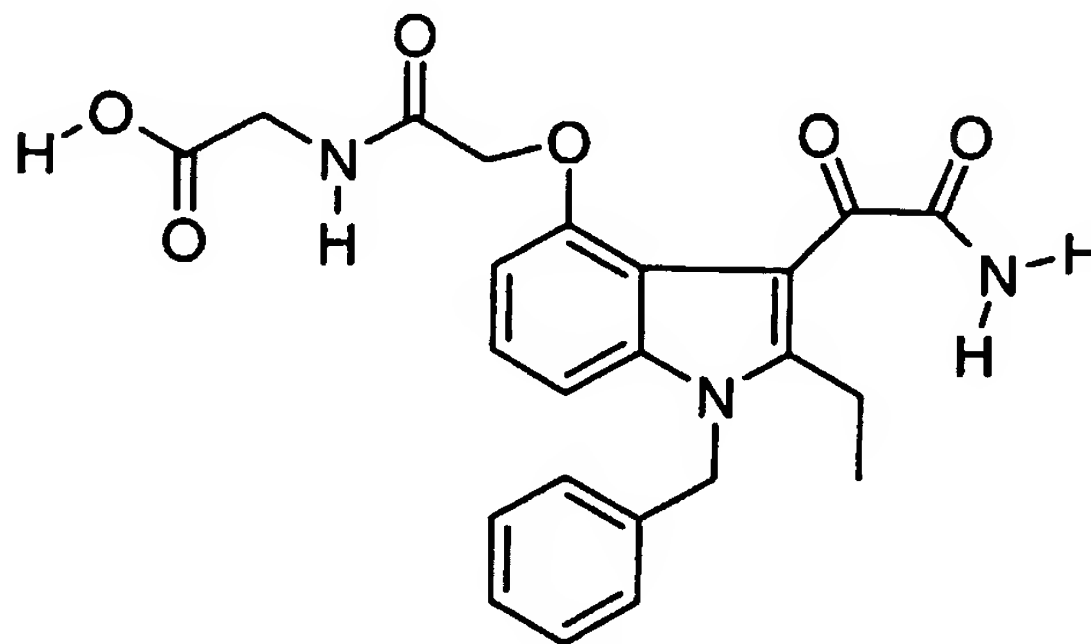
where R_{40} , R_{41} , R_{42} , and R_{43} are each independently selected from hydrogen or C_1 - C_8 alkyl.

-129-

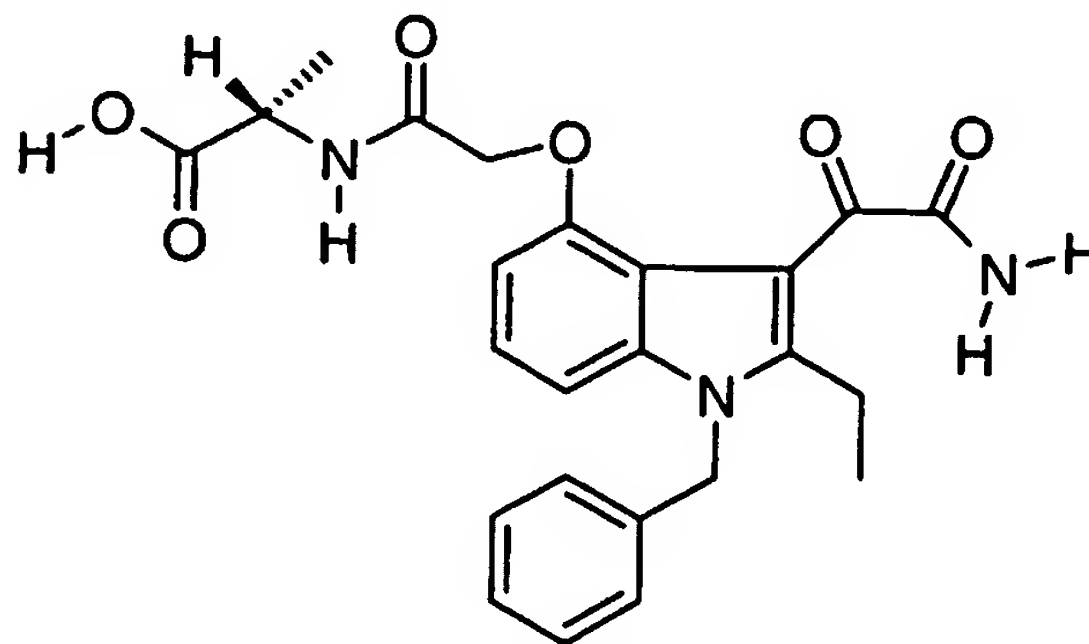
R₁₆ is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, and halo.

R₁₃ is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, phenyl, halophenyl, and halo, and t is an integer from 0 to 5.

20. An indole compound represented by the formulae
10 (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9),
(C10) or (C11);

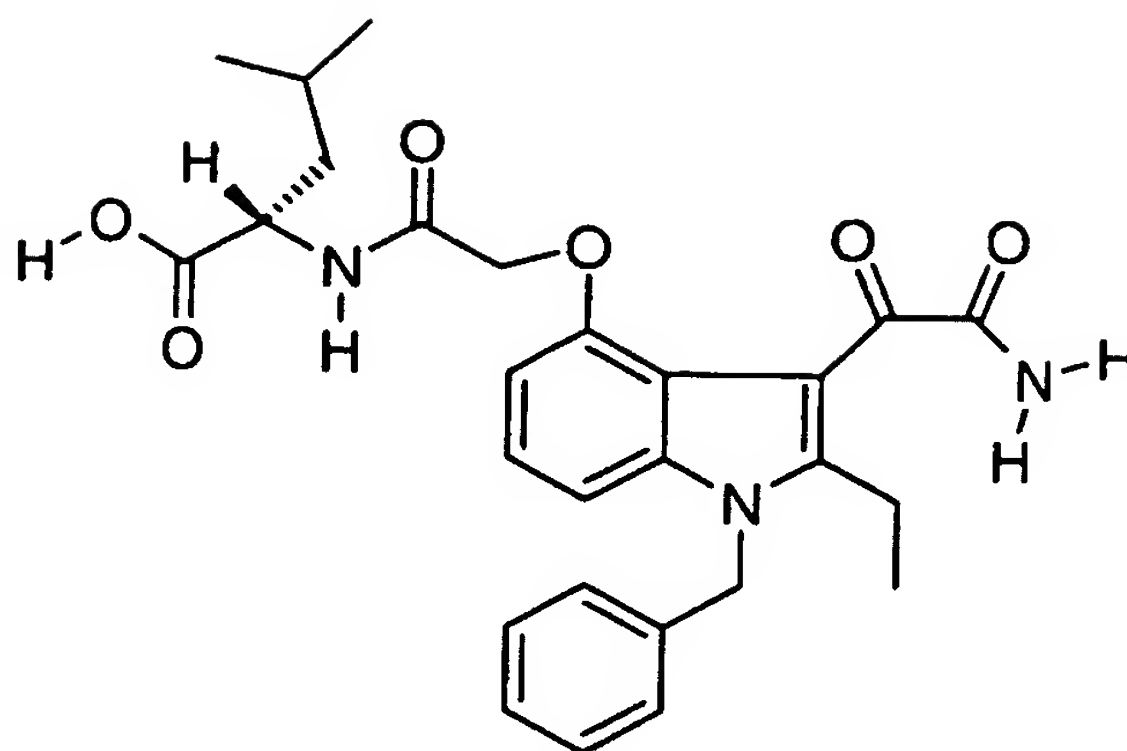


(C1),

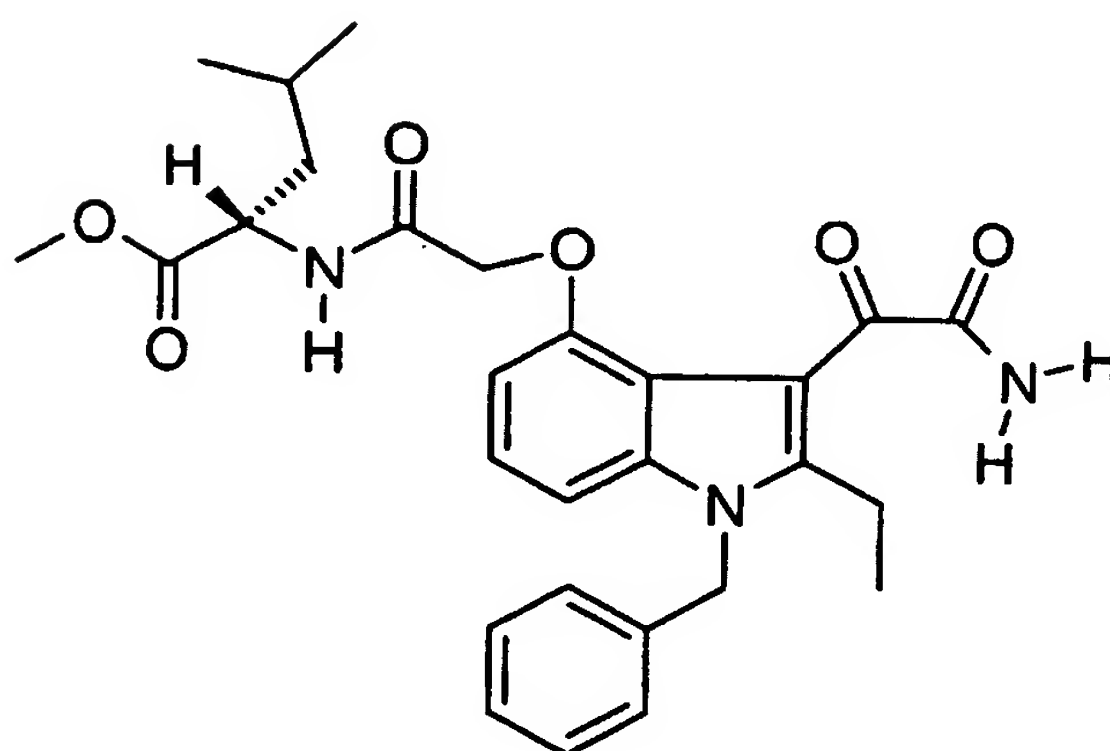


(C2) ,

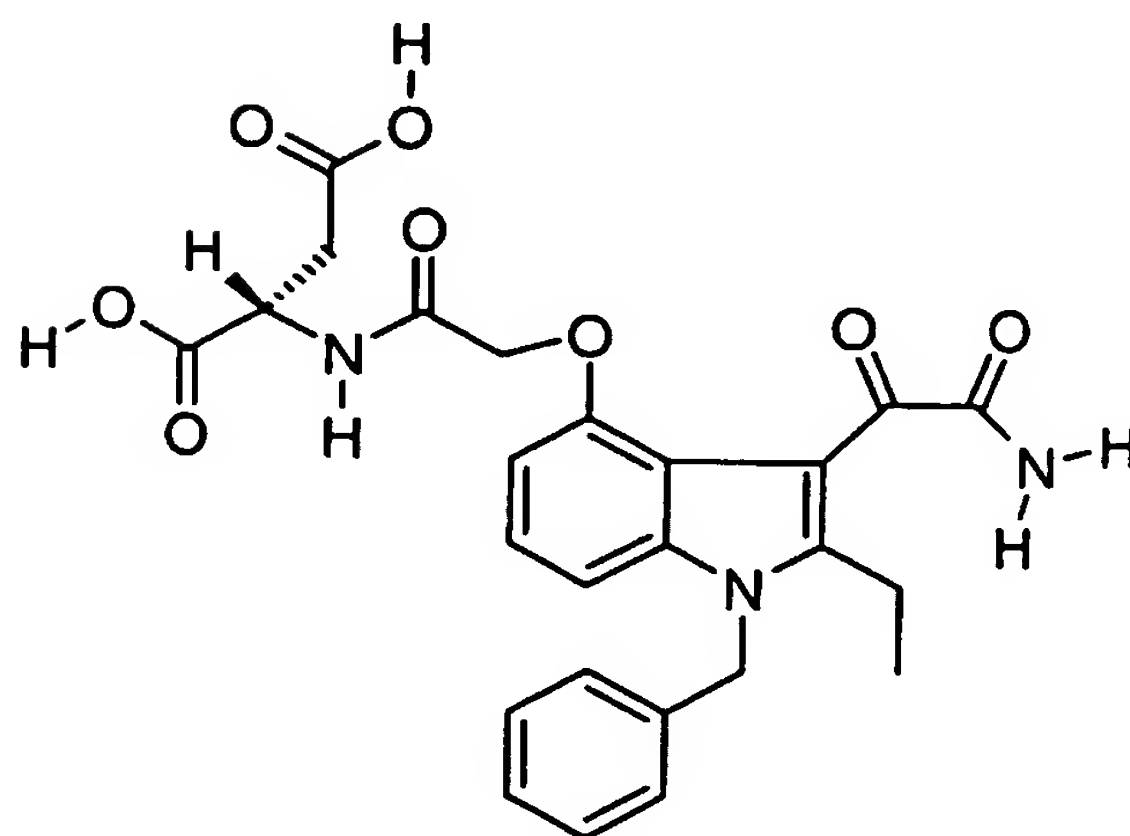
-130-



(C3) ,

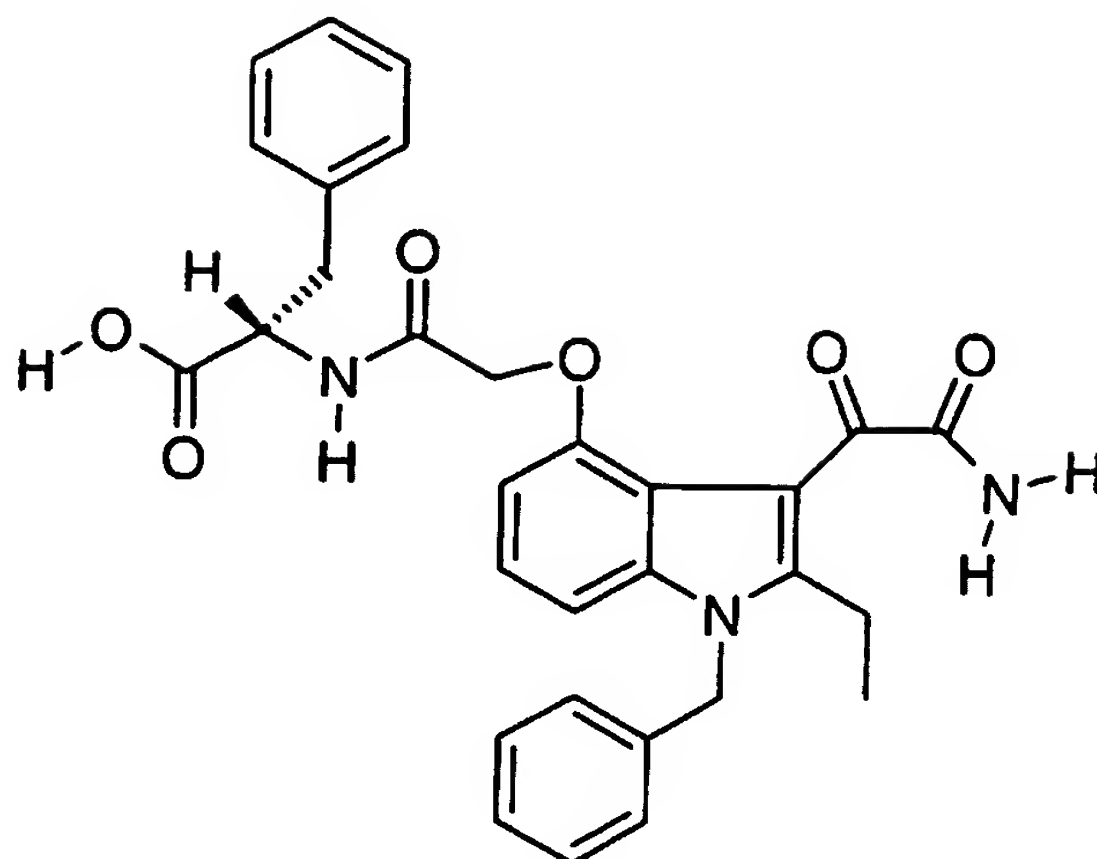


(C4) ,

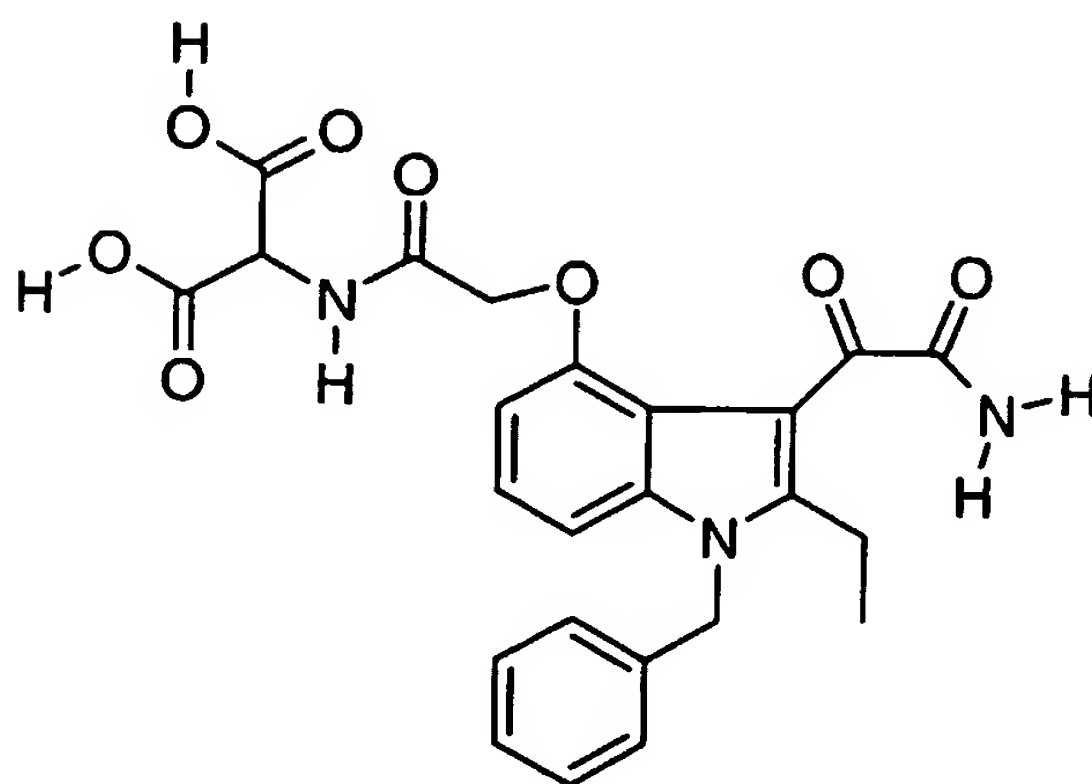


(C5) ,

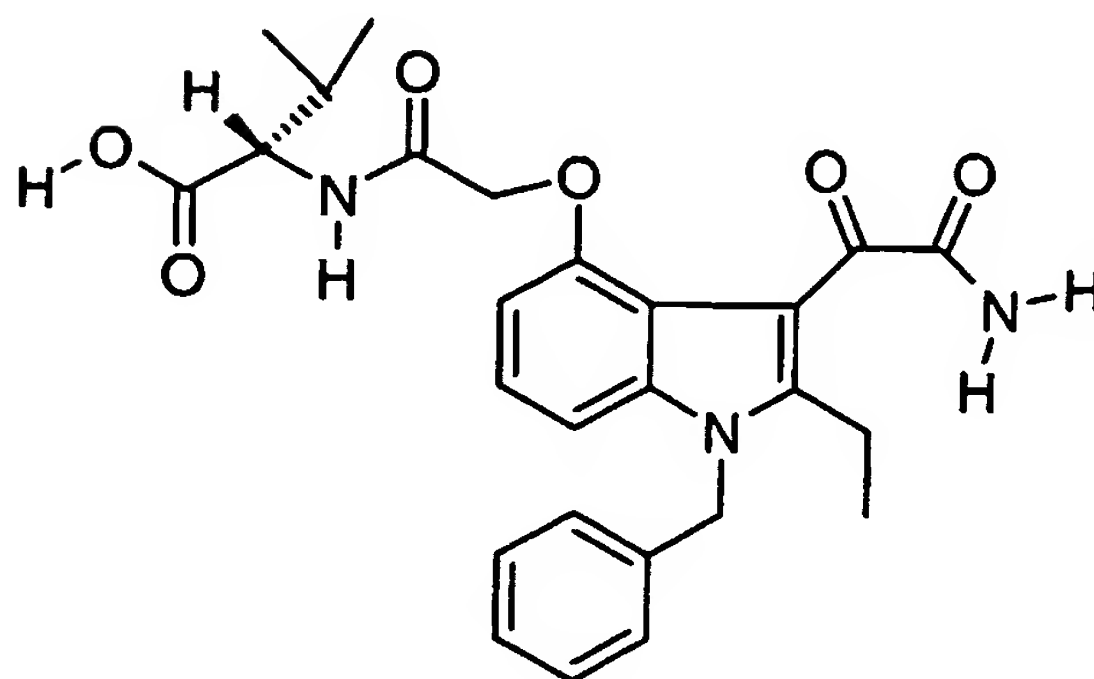
-131-



(C6) ,

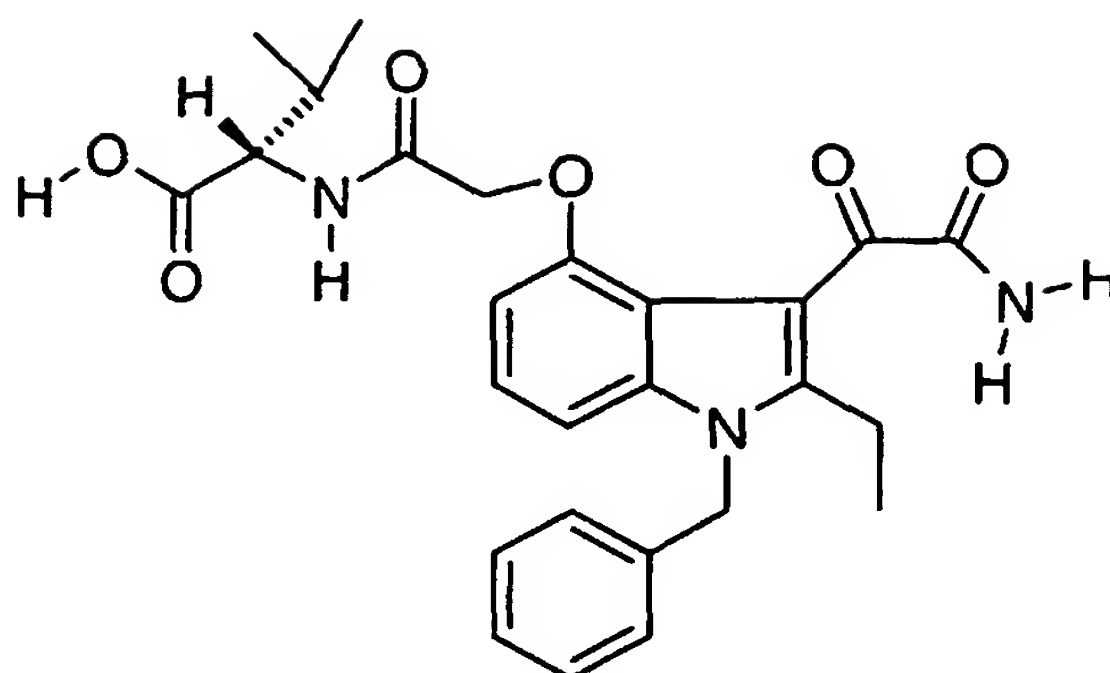


(C7) ,

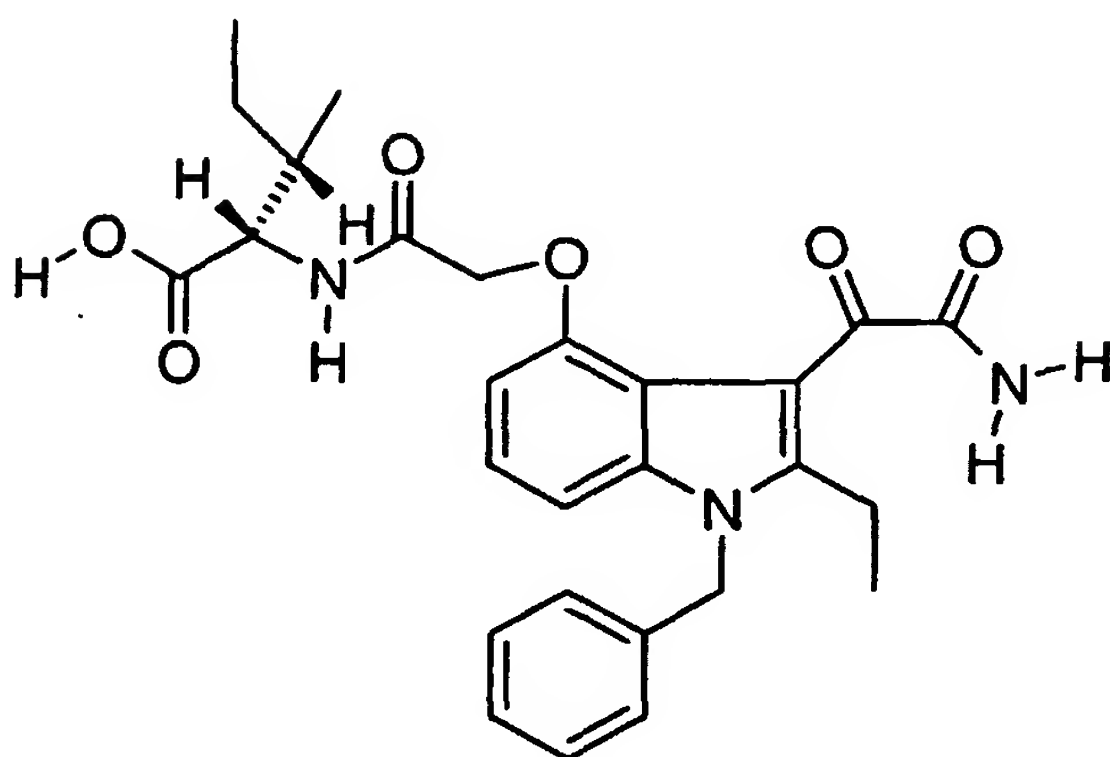


(C8) ,

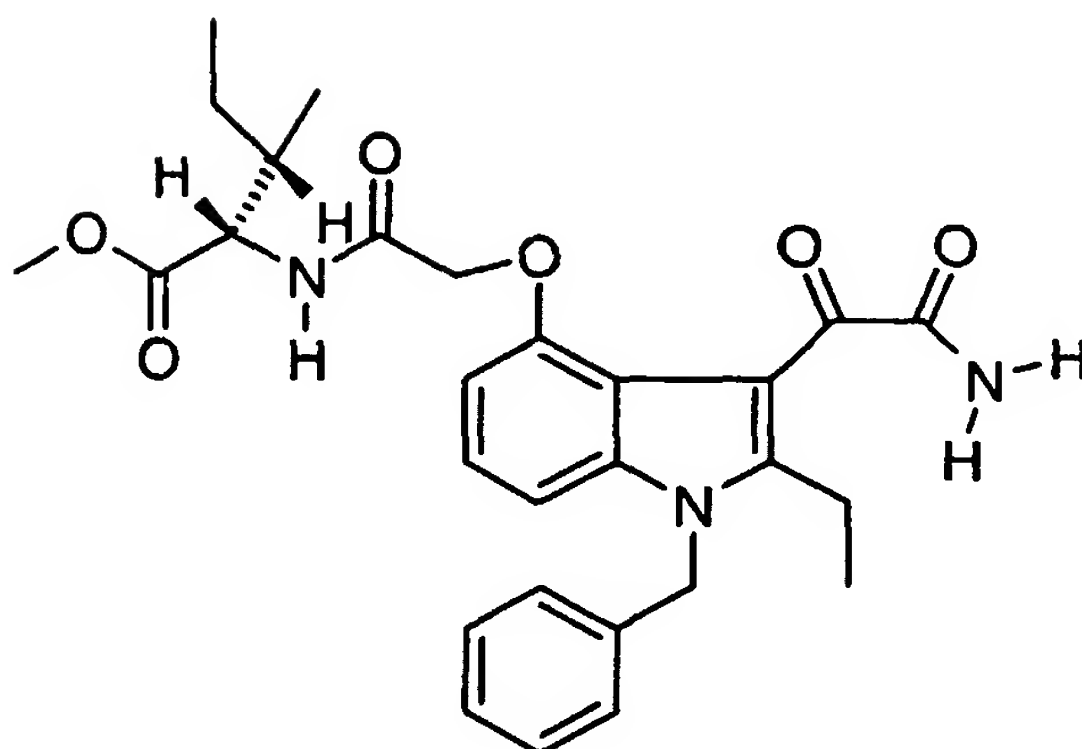
-132-



(C9) ,



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.

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21. A compound of claim 1 selected from the group consisting of:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

15 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

22. A pharmaceutical formulation comprising a indole
compound as claimed in claim 1 together with a
10 pharmaceutically acceptable carrier or diluent therefor.

23. A method of inhibiting sPLA₂ mediated release
of fatty acid which comprises contacting sPLA₂ with a
therapeutically effective amount of indole compound as
15 claimed in claim 1.

24. A method of treating a mammal, including a
human, to alleviate the pathological effects of
Inflammatory Diseases; wherein the method comprises
20 administration to said mammal of at least one indole
compound as claimed in Claim 1 in a pharmaceutically
effective amount.

25. A compound of claim 1 or a pharmaceutical
25 formulation containing an effective amount of the

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compound of claim 1 in treatment of Inflammatory Diseases.

26. A compound of claim 1 or a pharmaceutical
5 formulation containing an effective amount of the
compound of claim 1 for use as an inhibitor for
inhibiting sPLA₂ mediated release of fatty acid.

27. Use of a pharmaceutical composition comprising
10 sPLA₂ inhibitor compounds according to Claim 1 and
mixtures thereof for the manufacture of a medicament for
the therapeutic treatment of Inflammatory Diseases.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16319

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/22 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 675 110 A (LILLY CO ELI) 4 October 1995 (1995-10-04) cited in the application the whole document ---	1-26
Y	EP 0 620 215 A (LILLY CO ELI) 19 October 1994 (1994-10-19) cited in the application the whole document ---	1-26
Y	US 5 684 034 A (BACH NICHOLAS J ET AL) 4 November 1997 (1997-11-04) cited in the application the whole document ---	1-26
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

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Authorized officer

Frelon, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16319

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 00 37358 A (BACH NICHOLAS JAMES ;MORIN JOHN MICHAEL JUNIOR (US); LIN HO SHEN () 29 June 2000 (2000-06-29) the whole document ---	1-26
Y	WO 99 21559 A (DENNEY MICHAEL LYLE ;MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ---	1-26
Y	WO 99 21546 A (DENNEY MICHAEL LYLE ;MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ---	1-26
A, P	EP 0 952 149 A (LILLY CO ELI) 27 October 1999 (1999-10-27) the whole document ---	
A	WO 96 37469 A (MERCK FROSST CANADA INC ;LAU CHEUK K (CA); BLACK CAMERON (CA); GUA) 28 November 1996 (1996-11-28) abstract; claims ---	1-26
A	WO 91 06537 A (AMERICAN HOME PROD) 16 May 1991 (1991-05-16) abstract; claims ---	1-26
A	DILLARD R D ET AL: "INDOLE INHIBITORS OF HUMAN NONPANCREATIC SECRETORY PHOSPHOLIPASE A21. INDOLE-3-ACETAMIDES" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, no. 26, 20 December 1996 (1996-12-20), pages 5119-5136, XP002046054 ISSN: 0022-2623 the whole document -----	1-26

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-18 relate to an extremely large number of possible compounds. Unlimited and/or unspecified expressions like carbocyclic radical, heterocyclic radical, non-interfering substituents, a group containing 1 to 4 non-hydrogen atoms, a divalent linking group, aryl, aralkyl, acylamino acid, an acidic group or an organic substituents contain so many options, variables and possible permutations that the claims lack clarity and conciseness within the meaning of Article 6 PCT and arise to such an extent that a meaningful search of claims 1-18 is impossible. These claims have been therefore uncompletely searched.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the search is complete for claim 19 and dependent claims thereon on the basis of the illustrations by the examples wherein the following features appear constantly : R1 = benzyl; R2 = ethyl; R3 = CO-CO-NH₂; R5, R6, R7 = H; R4 = O-CH₂-CONH-aminoacid.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921559 A		EP 1039911 A	04-10-2000
WO 9921546 A	06-05-1999	AU 1279899 A	17-05-1999
		EP 1030661 A	30-08-2000
EP 0952149 A	27-10-1999	AU 2381799 A	28-10-1999
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		CN 1253948 A	24-05-2000
		CZ 9901369 A	17-11-1999
		CZ 9901370 A	17-11-1999
		EP 0950657 A	20-10-1999
		HU 9901220 A	28-04-2000
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		JP 11322713 A	24-11-1999
		JP 2000026416 A	25-01-2000
		NO 991821 A	18-10-1999
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		PL 332565 A	25-10-1999
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WO 9637469 A	28-11-1996	US 5604253 A	18-02-1997
		AU 5683296 A	11-12-1996
		CA 2219111 A	28-11-1996
WO 9106537 A	16-05-1991	AU 643996 B	02-12-1993
		AU 7740491 A	31-05-1991
		BR 9007790 A	15-09-1992
		CA 2070422 A	28-04-1991
		CA 2090042 A	28-04-1991
		EP 0502106 A	09-09-1992
		FI 921865 A	24-04-1992
		HU 63407 A	30-08-1993
		JP 5502222 T	22-04-1993
		PT 95692 A	13-09-1991
		US 5420289 A	30-05-1995
		US 5229516 A	20-07-1993

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-12420	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 16319	International filing date (day/month/year) 11/07/2000	(Earliest) Priority Date (day/month/year) 19/07/1999
Applicant ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

SPLA2 INHIBITOREN

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-18 relate to an extremely large number of possible compounds. Unlimited and/or unspecified expressions like carbocyclic radical, heterocyclic radical, non-interfering substituents, a group containing 1 to 4 non-hydrogen atoms, a divalent linking group, aryl, aralkyl, acylamino acid, an acidic group or an organic substituents contain so many options, variables and possible permutations that the claims lack clarity and conciseness within the meaning of Article 6 PCT and arise to such an extent that a meaningful search of claims 1-18 is impossible. These claims have been therefore uncompletely searched.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the search is complete for claim 19 and dependent claims thereon on the basis of the illustrations by the examples wherein the following features appear constantly : R1 = benzyl; R2 = ethyl; R3 = CO-CO-NH2; R5,R6,R7 = H; R4 = O-CH2-CONH-aminoacid.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16319

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/22 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 675 110 A (LILLY CO ELI) 4 October 1995 (1995-10-04) cited in the application the whole document ---	1-26
Y	EP 0 620 215 A (LILLY CO ELI) 19 October 1994 (1994-10-19) cited in the application the whole document ---	1-26
Y	US 5 684 034 A (BACH NICHOLAS J ET AL) 4 November 1997 (1997-11-04) cited in the application the whole document --- -/--	1-26

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Frelon, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16319

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 00 37358 A (BACH NICHOLAS JAMES ;MORIN JOHN MICHAEL JUNIOR (US); LIN HO SHEN () 29 June 2000 (2000-06-29) the whole document ---	1-26
Y	WO 99 21559 A (DENNEY MICHAEL LYLE ;MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ---	1-26
Y	WO 99 21546 A (DENNEY MICHAEL LYLE ;MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ---	1-26
A,P	EP 0 952 149 A (LILLY CO ELI) 27 October 1999 (1999-10-27) the whole document ---	
A	WO 96 37469 A (MERCK FROSST CANADA INC ;LAU CHEUK K (CA); BLACK CAMERON (CA); GUA) 28 November 1996 (1996-11-28) abstract; claims ---	1-26
A	WO 91 06537 A (AMERICAN HOME PROD) 16 May 1991 (1991-05-16) abstract; claims ---	1-26
A	DILLARD R D ET AL: "INDOLE INHIBITORS OF HUMAN NONPANCREATIC SECRETORY PHOSPHOLIPASE A21. INDOLE-3-ACETAMIDES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, no. 26, 20 December 1996 (1996-12-20), pages 5119-5136, XP002046054 ISSN: 0022-2623 the whole document -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0675110	A	04-10-1995	AU 688458 B	12-03-1998
			AU 1621795 A	12-10-1995
			BR 9501404 A	05-03-1996
			CA 2146097 A	02-10-1995
			CN 1114310 A	03-01-1996
			CZ 9500822 A	13-12-1995
			FI 951553 A	02-10-1995
			HU 72048 A	28-03-1996
			JP 7285933 A	31-10-1995
			NO 951252 A	02-10-1995
			NZ 270848 A	26-05-1997
			PL 307951 A	02-10-1995
			RU 2128169 C	27-03-1999
			US 5654326 A	05-08-1997
			US 5733923 A	31-03-1998
			US 5919810 A	06-07-1999
			US 5919943 A	06-07-1999
			ZA 9502693 A	30-09-1996
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EP 0620215	A	19-10-1994	AT 183503 T	15-09-1999
			AU 676884 B	27-03-1997
			AU 5949294 A	20-10-1994
			BR 9401482 A	18-10-1994
			CA 2121323 A	17-10-1994
			CN 1098715 A	15-02-1995
			CZ 9400893 A	15-12-1994
			DE 69420068 D	23-09-1999
			DE 69420068 T	23-12-1999
			ES 2138648 T	16-01-2000
			FI 941767 A	17-10-1994
			HU 70836 A	28-11-1995
			JP 7025850 A	27-01-1995
			NO 941361 A	17-10-1994
			NZ 260298 A	28-05-1996
			US 5684034 A	04-11-1997
			ZA 9402615 A	16-10-1995
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US 5684034	A	04-11-1997	AT 183503 T	15-09-1999
			AU 676884 B	27-03-1997
			AU 5949294 A	20-10-1994
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			EP 0620215 A	19-10-1994
			ES 2138648 T	16-01-2000
			FI 941767 A	17-10-1994
			HU 70836 A	28-11-1995
			JP 7025850 A	27-01-1995
			NO 941361 A	17-10-1994
			NZ 260298 A	28-05-1996
			ZA 9402615 A	16-10-1995
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WO 0037358	A	29-06-2000	AU 2373600 A	12-07-2000
<hr/>				
WO 9921559	A	06-05-1999	AU 1200899 A	17-05-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921559 A		EP 1039911 A	04-10-2000
WO 9921546 A	06-05-1999	AU 1279899 A	17-05-1999
		EP 1030661 A	30-08-2000
EP 0952149 A	27-10-1999	AU 2381799 A	28-10-1999
		AU 2381999 A	28-10-1999
		BR 9901279 A	02-05-2000
		CN 1253948 A	24-05-2000
		CZ 9901369 A	17-11-1999
		CZ 9901370 A	17-11-1999
		EP 0950657 A	20-10-1999
		HU 9901220 A	28-04-2000
		HU 9901221 A	28-04-2000
		JP 11322713 A	24-11-1999
		JP 2000026416 A	25-01-2000
		NO 991821 A	18-10-1999
		NO 991822 A	18-10-1999
		PL 332565 A	25-10-1999
		PL 332566 A	25-10-1999
WO 9637469 A	28-11-1996	US 5604253 A	18-02-1997
		AU 5683296 A	11-12-1996
		CA 2219111 A	28-11-1996
WO 9106537 A	16-05-1991	AU 643996 B	02-12-1993
		AU 7740491 A	31-05-1991
		BR 9007790 A	15-09-1992
		CA 2070422 A	28-04-1991
		CA 2090042 A	28-04-1991
		EP 0502106 A	09-09-1992
		FI 921865 A	24-04-1992
		HU 63407 A	30-08-1993
		JP 5502222 T	22-04-1993
		PT 95692 A	13-09-1991
		US 5420289 A	30-05-1995
		US 5229516 A	20-07-1993

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED

<p>To:</p> <p>GINAH, Francis O. ELI LILLY AND COMPANY Lilly Corporate Center Indianapolis, Indiana 46285 ETATS-UNIS D'AMERIQUE</p>	<p>JUL 03 2001</p> <p>ELI LILLY & COMPANY PATENT DIVISION</p>
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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing (day/month/year)	28.06.2001
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Applicant's or agent's file reference X-12420
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IMPORTANT NOTIFICATION

International application No PCT/US00/16319	International filing date (day/month/year) 11/07/2000	Priority date (day/month/year) 19/07/1999
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Applicant ELI LILLY AND COMPANY et al
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1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Handwritten signature/initials

<p>Name and mailing address of the IPEA/</p> <p> European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx 523656 epmu d Fax +49 89 2399 - 4465</p>	<p>Authorized officer</p> <p>Ambroa, J.R.</p> <p>Tel +49 89 2399-8012</p>
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-12420		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/16319	International filing date (day/month/year) 11/07/2000	Priority date (day/month/year) 19/07/1999	
International Patent Classification (IPC) or national classification and IPC C07D209/22			
Applicant ELI LILLY AND COMPANY et al			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 136 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input checked="" type="checkbox"/> Certain documents citedVII <input checked="" type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 19/01/2001		Date of completion of this report 28.06.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx. 523656 epmu d Fax +49 89 2399 - 4465		Authorized officer Feiler, L Telephone No +49 89 2399 8282 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/16319

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-109 as received on 13/06/2001 with letter of 11/06/2001

Claims, No.:

1-26 as received on 13/06/2001 with letter of 11/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/16319

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-18, 21-26.

because:

☒ the said international application, or the said claims Nos. 22, 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-18, 21, 24-26.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19, 20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	19, 20
Industrial applicability (IA)	Yes:	Claims	19, 20

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/16319

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/16319

1. With letter of 11/06/01 the Applicant has filed a "replacement application comprising description pages 1-109 and Claims 1-26. It would appear that these documents do not indicate the amendments indicated in the response to the written opinion dated 16/03/0; they are essentially identical to the document originally filed.

2. Claims 22 and 23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

It has to be stressed that subject matter of Claims 1-18 has not been searched completely. Consequently, the following observations apply to **subject matter of Claim 19** and dependent claims only.

3. Cited Documents

EP-A-0675110= D1

EP-A-0620215= D2

US-A-5684034= D3

WO-A-0037358= D4

WO-A-9921559= D5

WO-A-9921546= D6

EP-A-0952149= D7

WO-A-9637469= D8

WO-A-9106537= D9

J. Med. Chem. 39(1996), pp. 5119-5139= D10

The indicated designation will be used throughout the examination procedure.

D4 and D7 are P-documents.

4. Novelty

The subject-matter of Claim 19 differs from D1 essentially due to the fact that the 4-position of the indole moiety is substituted by an acidic group (e.g. -COOH) whereas the corresponding position of the compounds of Claim 19 of the application comprises a carbamoyl group.

D2, D3 and D6 disclose indole-3-acetamid derivatives whereas the compounds of Claim 19 of the application are indole-3-glyoxylamides.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/16319

According to D4 the 3-indole substituent is an oxime amide or oxime thioamide. D5 refers to a specific indol-4-yloxyacetic morpholino-N-ethylester.

D7 discloses carbazole derivatives, D8 refers to N-benzylindol-3-yl propanoic acid, D10 discloses indole-3-acetamides and D9 comprises indole derivatives not considered according to the application.

The subject-matter claimed can therefore be considered novel.

5. Inventive Step - Breadth of Claims

5.1 Subjective Problem

According to the application (p. 1, first paragraph and page 2, lines 14-16) the problem underlying the invention is to be seen in the provision of further compounds which are inhibitors of mammalian secretory phospholipase A₂ (sPLA₂) and are therefore useful to treat inflammatory diseases.

5.2 Relevant and closest prior art

Documents D1-D3, D5, D6, D9 and D10 are considered to be relevant for the assessment of inventive step since these compounds come structurally close to those comprised by Claim 19 of the application and also have the same qualitative activity. If the claimed priority date is not valid D4 may also come into picture.

The closest prior art is given by D1.

5.3 Objectively solved problem

The application documents disclose the test methodology and quantitative test data according to the table of page 109 so that it can be said that at least the tested compounds solve the problem defined above.

5.4 Evaluation of the solution of the problem

D1-D3, D5, D6, D9 and D10 disclose compounds structurally very similar to those of the present application.

The products of those documents also solve the problem of providing compounds which inhibit mamalian sPLA₂.

The person skilled in the art seeking a solution to the problem defined above would therefore have been prompted to consider further derivatives of compounds which are already known to solve the above defined problem. In this context it is to be stressed that e.g. D1 discloses that the R⁴ corresponding substituent is an acidic group e.g. the -COOH group, but D5 and D6 disclose that this group can be derivatised (ester functions) without changing the qualitative activity. In other words the compounds of D5

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/16319

and D6 could be considered as prodrugs of D1-compounds. Consequently, the compounds of the invention being amide derivatives are to be considered as further prodrugs of D1-compounds.

The person skilled in the art would have been able to infer that a modification of the proposed type would have no effect on the activity profile so that he would have considered the proposed solution in the expectation of success.

The solution of the technical problem defined in point 5.1 according to the application is therefore obvious in the light of the prior art and thus the subject-matter of the present Claim 19 cannot be considered to be inventive.

6. Industrial applicability

For the assessment of the present claims 22 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7. Clairity

- In Claim 19 (L_4) remains undefined
- Claim 20 appears twice; specific compounds are claimed in the second Claim 20 already claimed in the first one; this is considered to be superfluous and should be avoided.
- Claim 24 is unclear.

8. Suggestions

In a possible national or regional examination procedure an inventive step could possibly be acknowledged should comparative data be submitted which show that apart from the technical problem defined in point 4.1 another, e.g. more exacting, problem, which can be derived from the application as originally filed (e.g. surprising improvement), existed and has actually been solved by originally disclosed technical

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/16319

features, which would need to be incorporated in Claim 19.

In this respect it should be borne in mind that the compounds of the closest prior D1 must bear the closest possible structural resemblance in order that the comparison be valid. A suitable comparison would be e.g.:

Examples 1 and 17 of D1 versus corresponding compounds of the application whereby all possible variations should be included.

The breadth of the claims should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based.

Even if it turns out that the tested compounds of page 109 solve the problem defined in point 8, first paragraph the proposed broadness goes far beyond of what could be considered to be a reasonable generalisation:

L_4 is always $-OCH_2-$;

R_b is the residue of simple amino acids only;

$(R_{13})_t$ is always H;

R_{16} is H and

R^{22} is an alkyl only.

It is not reasonable e.g. to define NR_b as "an amino acid residue of a natural or unnatural amino acid" or to define L_4 (which was obviously intended to mean (Lc)) other than $-OCH_2-$.

The description should be adapted to new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

All the documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.

172

10/018,037

10018037

Page 1

08/18/2002

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1626gms

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 Apr 08 "Ask CAS" for self-help around the clock
NEWS 3 Apr 09 BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4 Apr 09 ZDB will be removed from STN
NEWS 5 Apr 19 US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6 Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available
NEWS 9 Jun 03 New e-mail delivery for search results now available
NEWS 10 Jun 10 MEDLINE Reload
NEWS 11 Jun 10 PCTFULL has been reloaded
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;
saved answer sets no longer valid
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY
NEWS 15 Jul 30 NETFIRST to be removed from STN
NEWS 16 Aug 08 CANCERLIT reload
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18 Aug 08 NTIS has been reloaded and enhanced
NEWS 19 Aug 09 JAPIO to be reloaded August 18, 2002

NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,
CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'HOME' ENTERED AT 09:30:57 ON 18 AUG 2002

Golam Shameem

=> FIL REGISTRY
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

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DICTIONARY FILE UPDATES: 16 AUG 2002 HIGHEST RN 444143-26-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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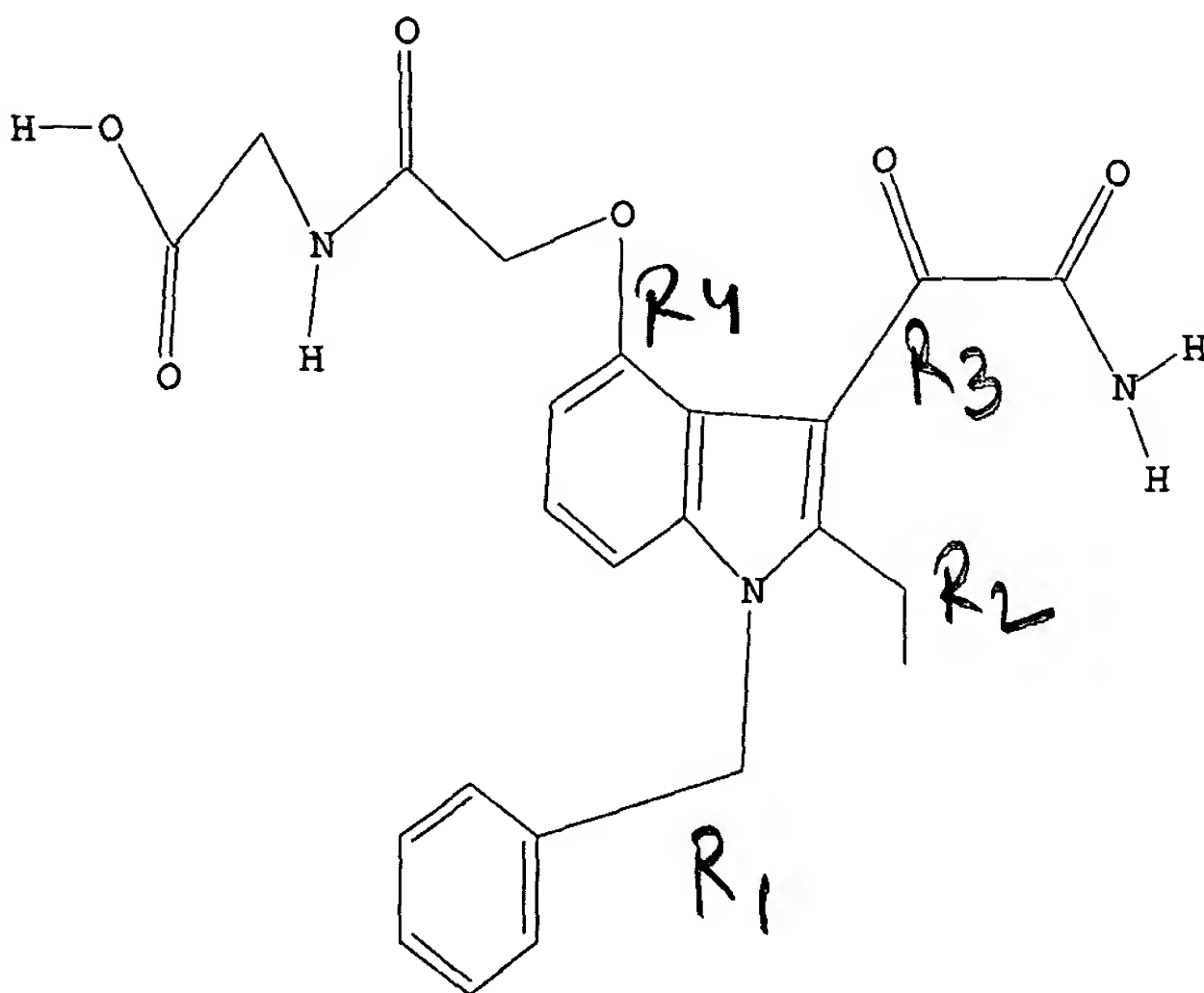
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Calculated physical property data is now available. See HELP PROPERTIES
for more information. See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>
Uploading 10018037.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

Golam Shameem

=> s l1

SAMPLE SEARCH INITIATED 09:31:40 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS
SEARCH TIME: 00.00.01

1 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 9 TO 360
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> FIL CAPLUS

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.38	0.59

FULL ESTIMATED COST

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=> d his

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L1 STRUCTURE UPLOADED

L2 1 S L1

FILE 'CAPLUS' ENTERED AT 09:31:48 ON 18 AUG 2002

=> s l1

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...

Golam Shameem

Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

SAMPLE SEARCH INITIATED 09:32:04 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS
SEARCH TIME: 00.00.01

1 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 9 TO 360
PROJECTED ANSWERS: 1 TO 80

L3 1 SEA SSS SAM L1

L4 1 L3

=> FIL REGISTRY
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.40	1.77

FULL ESTIMATED COST

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=> s l1 sss full
FULL SEARCH INITIATED 09:32:31 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 164 TO ITERATE

100.0% PROCESSED 164 ITERATIONS
SEARCH TIME: 00.00.01

8 ANSWERS

L5 8 SEA SSS FUL L1

=> FIL CAPLUS
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION

Golam Shameem

FULL ESTIMATED COST

140.28

142.05

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=> s 15

L6

1 L5

=> d ibib abs hitstr 16 tot

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63970 CAPLUS

DOCUMENT NUMBER: 134:116236

TITLE: Preparation of indole amino acid derivatives as secretory phospholipase A2 (sPLA2) inhibitors

INVENTOR(S): Lin, Ho-Shen; Richett, Michael Enrico

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 142 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

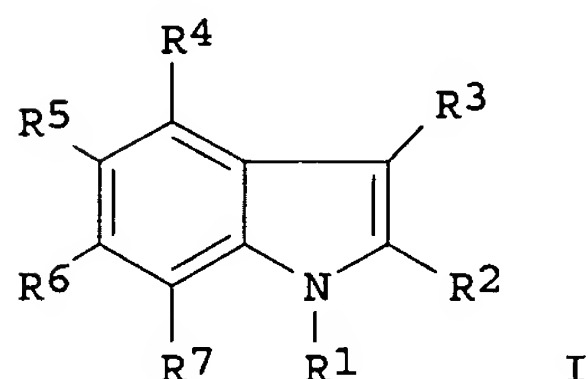
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005761	A1	20010125	WO 2000-US16319	20000711
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

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EP 1202963 A1 20020508 EP 2000-944673 20000711
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL
 PRIORITY APPLN. INFO.: US 1999-144502P P 19990719
 WO 2000-US16319 W 20000711
 OTHER SOURCE(S): MARPAT 134:116236
 GI



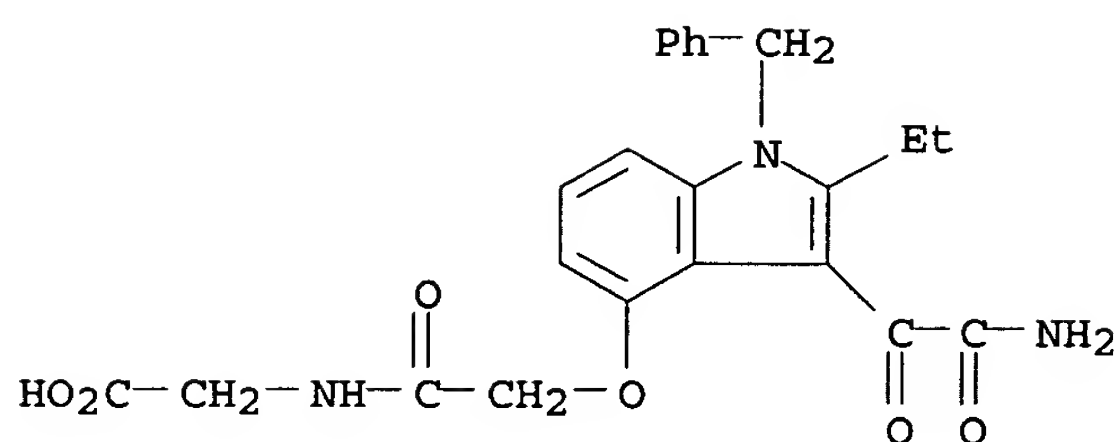
AB Indole derivs. I [R1 = (un)substituted alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, or heterocyclyl connected directly or via a divalent linking group to the indole ring; R2 is H or a group contg. 1-4 non-hydrogen atoms plus any required hydrogen atoms; R3 is -L3-Z, where L3 is a bond, CH2, O, S, NH, or CO and Z is -C(:NORa)C(:X)NH2, -C(:X)CONH2, or CRa2C(:X)NH2 (X = O or S and Ra = alkyl, aryl, alkaryl, alkoxy, aralkyl, CN); R4 is the group -(Lc)-(acylamino acid group), where Lc is an acylamino acid linker; R5 is H, a non-interfering substituent, or the group -(La)-(acidic group), where La is an acid linker; R6, R7 = H, a non-interfering substituent or (un)substituted carbocyclyl] were prepd. for inhibiting sPLA2 mediated release of fatty acids for treatment of inflammatory diseases such as septic shock. Thus, treatment of N-tert-butoxycarbonyl-3-methoxy-2-methylaniline with N-methoxy-N-methylpropanamide and then trifluoroacetic acid afforded 2-ethyl-4-methoxy-1H-indole. N-benylation, O-demethylation, alkylation with Me bromoacetate, reaction with oxalyl chloride and ammonia gave [[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid Me ester (1). Reaction of 1 with glycine Me ester hydrochloride and sapon. afforded N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine (3a). Compds. 1 and 3a resp. showed IC50 = 49 and 71 nM for inhibition of human secreted PLA2.

IT 321153-17-7P 321153-19-9P 321153-21-3P
 321153-23-5P 321153-25-7P 321153-27-9P
 321153-29-1P 321153-31-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of indole amino acid derivs. as secretory phospholipase A2 (sPLA2) inhibitors)

RN 321153-17-7 CAPLUS

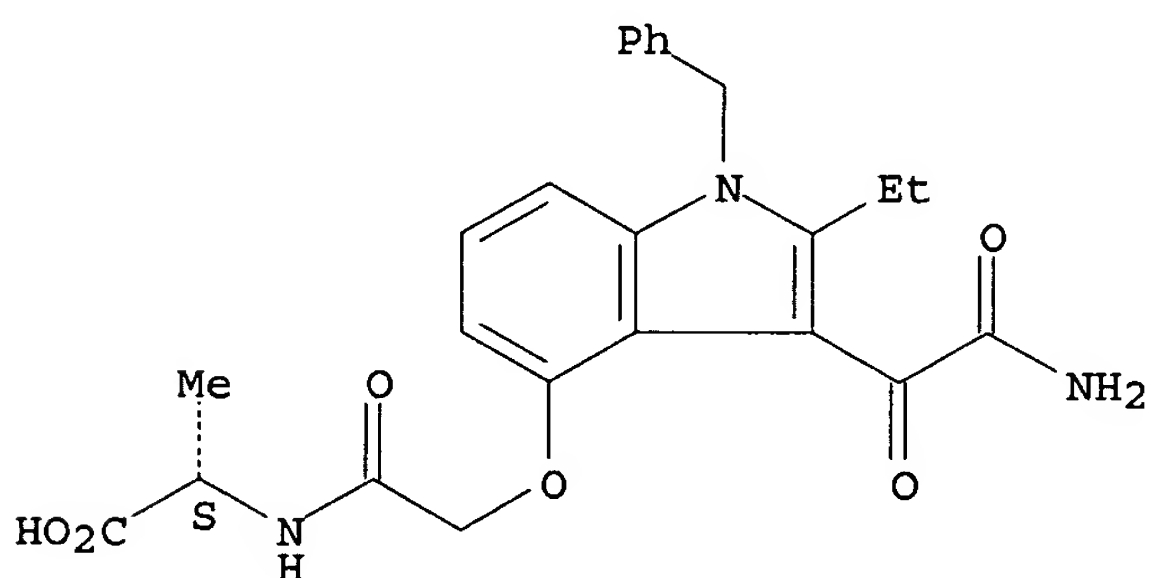
CN Glycine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)



RN 321153-19-9 CAPLUS

CN L-Alanine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

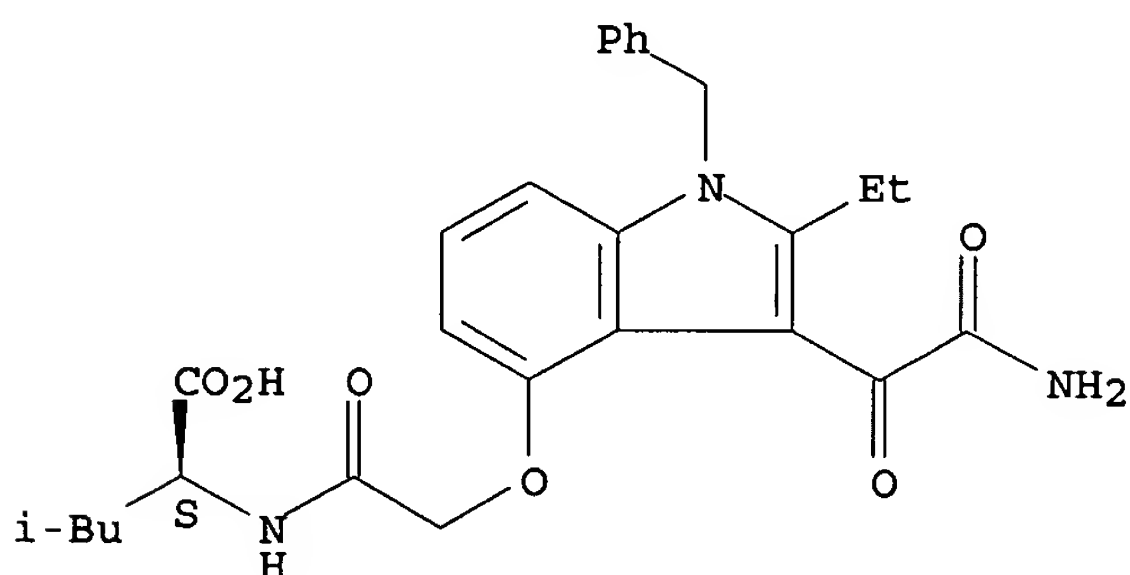
Absolute stereochemistry.



RN 321153-21-3 CAPLUS

CN L-Leucine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

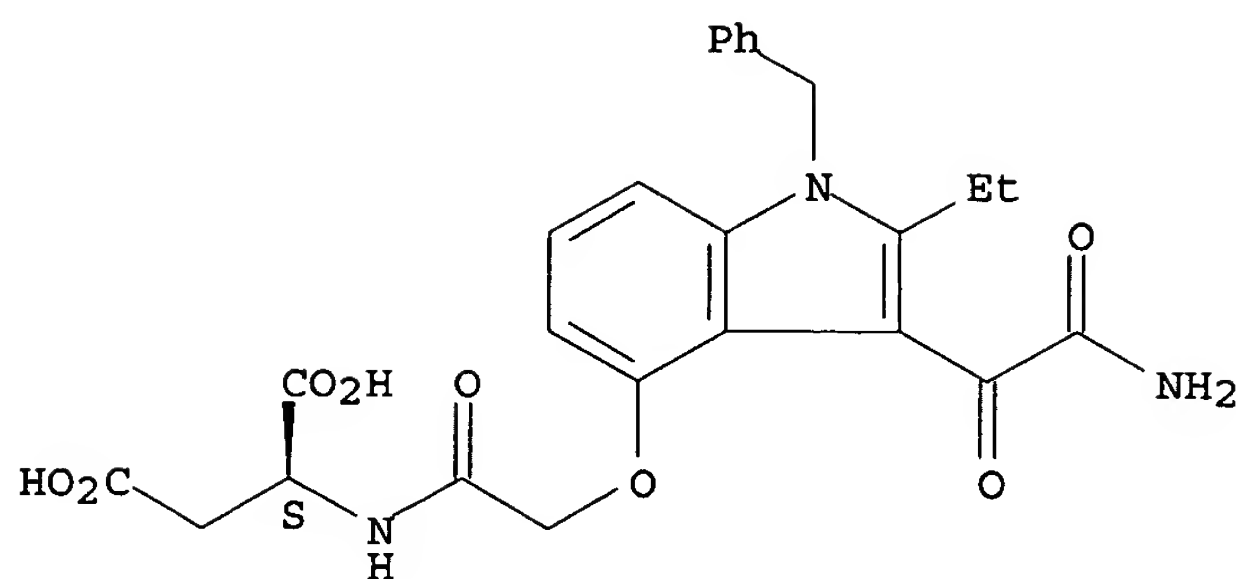
Absolute stereochemistry.



RN 321153-23-5 CAPLUS

CN L-Aspartic acid, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

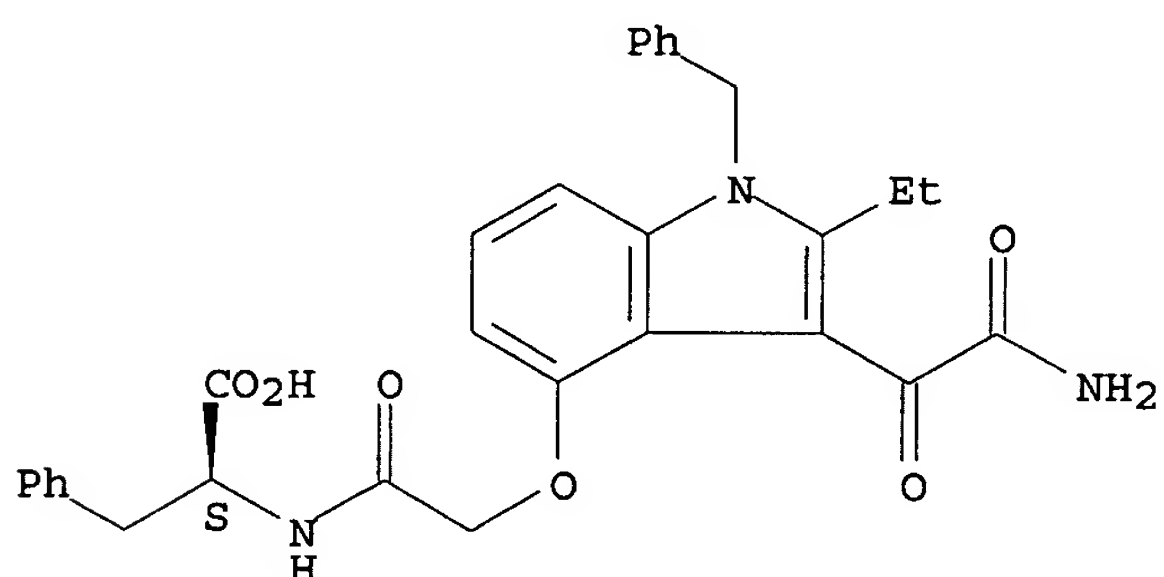
Absolute stereochemistry.



RN 321153-25-7 CAPLUS

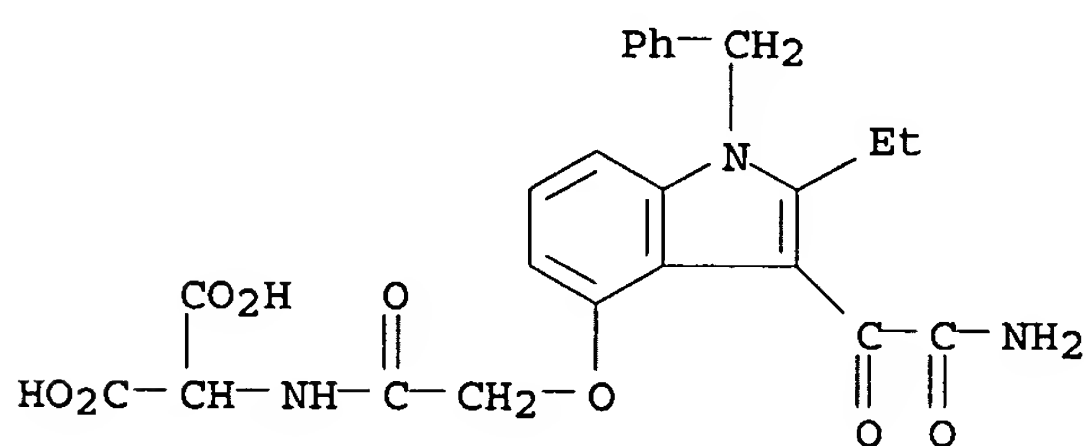
CN L-Phenylalanine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 321153-27-9 CAPLUS

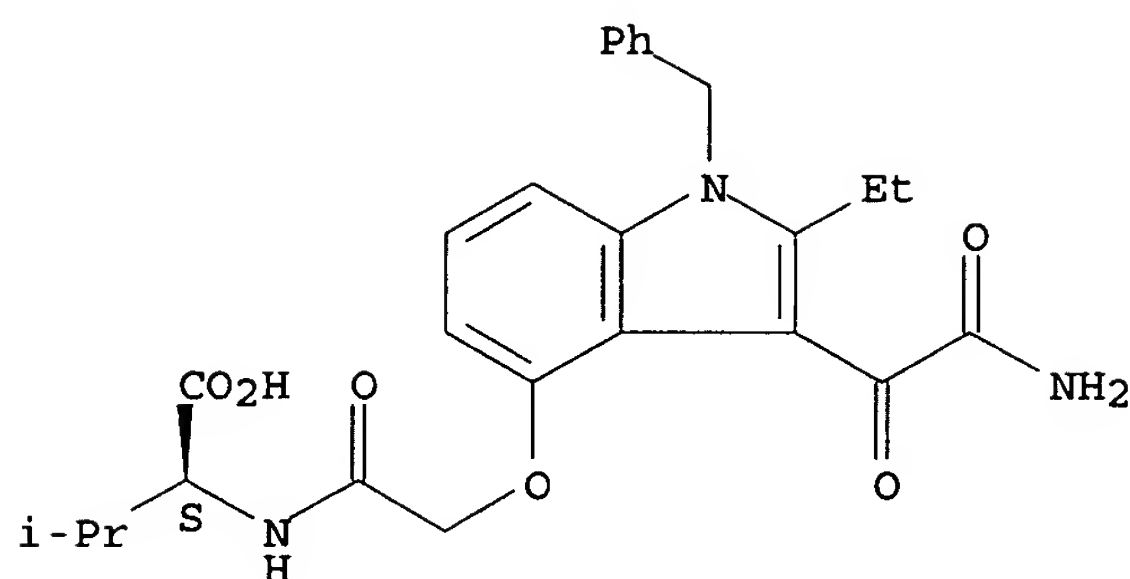
CN Propanedioic acid, [[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]amino]- (9CI) (CA INDEX NAME)



RN 321153-29-1 CAPLUS

CN L-Valine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

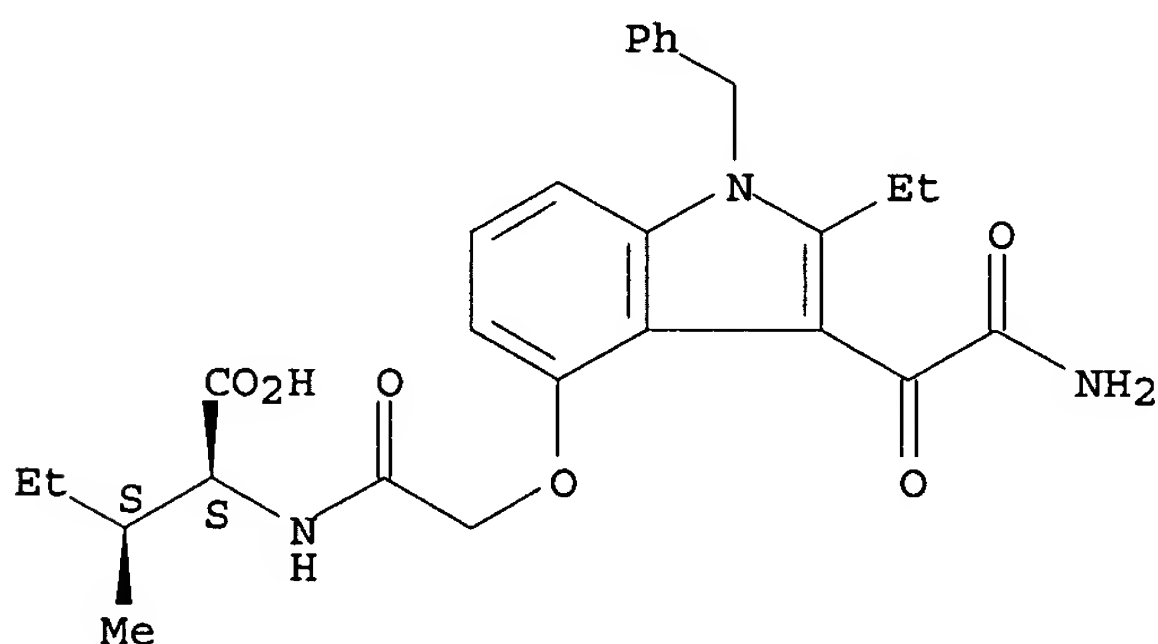
Absolute stereochemistry.



RN 321153-31-5 CAPLUS

CN L-Isoleucine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL REGISTRY

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

5.58

147.63

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

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-0.62

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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

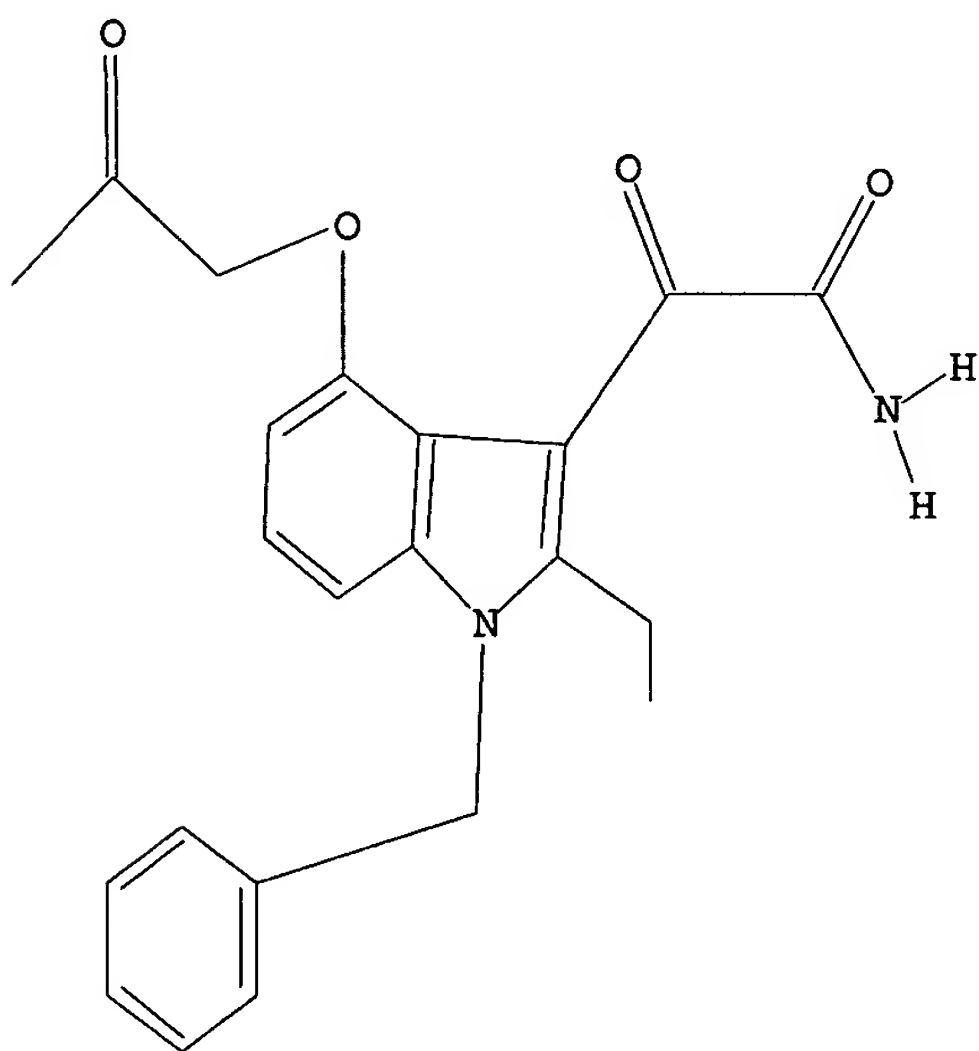
Uploading 10018037a.str

L7 STRUCTURE UPLOADED

=> d 17

L7 HAS NO ANSWERS

L7 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 17

SAMPLE SEARCH INITIATED 09:34:49 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

BATCH **COMPLETE**

PROJECTED ITERATIONS: 9 TO 360

PROJECTED ANSWERS: 0 TO 0

L8 0 SEA SSS SAM L7

=> s 17 sss full

Golam Shameem

0 ANSWERS

FULL SEARCH INITIATED 09:35:05 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 164 TO ITERATE

100.0% PROCESSED 164 ITERATIONS
SEARCH TIME: 00.00.01

0 ANSWERS

L9 0 SEA SSS FUL L7

=>

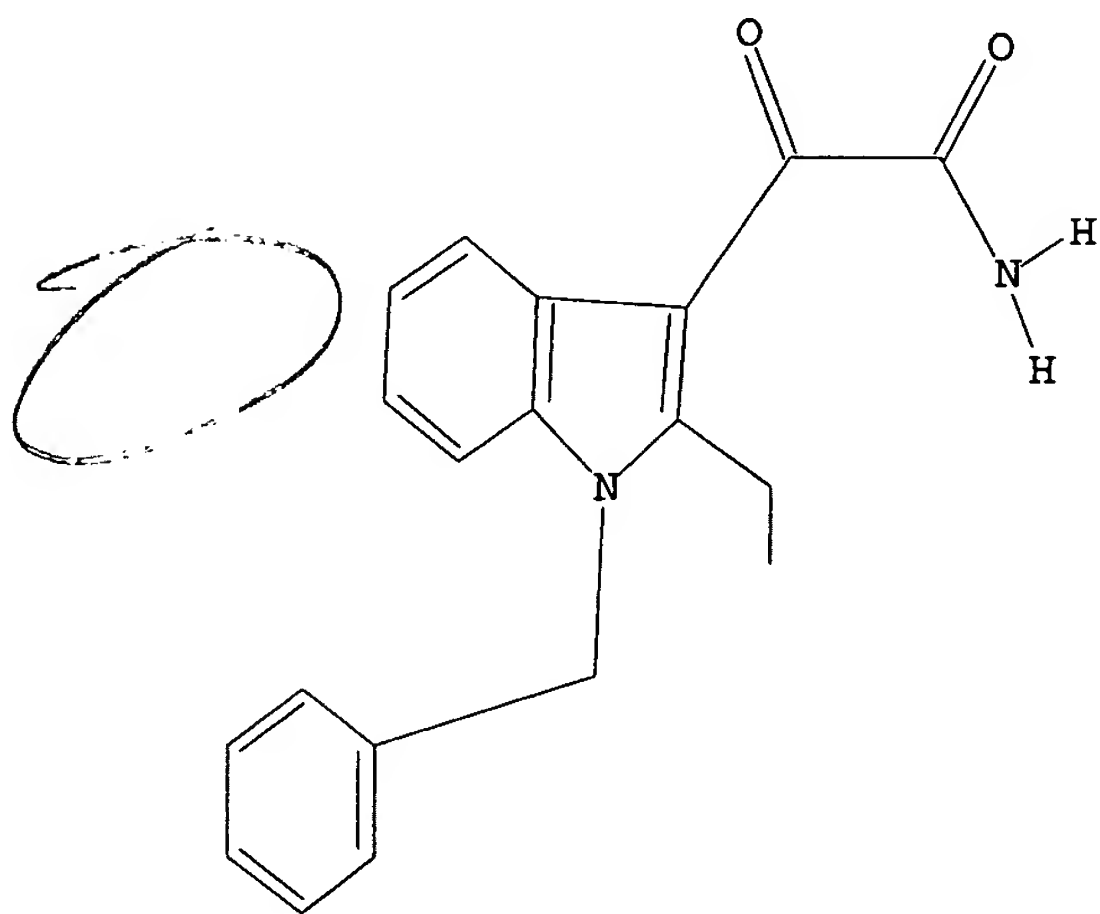
Uploading 10018037b.str

L10 STRUCTURE UPLOADED

=> d l10

L10 HAS NO ANSWERS

L10 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l10

SAMPLE SEARCH INITIATED 09:36:41 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 10 TO ITERATE

100.0% PROCESSED 10 ITERATIONS
SEARCH TIME: 00.00.01

6 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**

PROJECTED ITERATIONS: 11 TO 389
PROJECTED ANSWERS: 6 TO 266

L11 6 SEA SSS SAM L10

=> s l10 sss full

FULL SEARCH INITIATED 09:36:51 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 209 TO ITERATE

Golam Shameem

08/18/2002

100.0% PROCESSED 209 ITERATIONS
SEARCH TIME: 00.00.01

136 ANSWERS

L12 136 SEA SSS FUL L10

=> FIL CAPLUS
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE ENTRY	TOTAL SESSION
281.70	429.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
0.00	-0.62

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=> d his

(FILE 'HOME' ENTERED AT 09:30:57 ON 18 AUG 2002)

FILE 'REGISTRY' ENTERED AT 09:31:16 ON 18 AUG 2002

L1 STRUCTURE UPLOADED
L2 1 S L1

FILE 'CAPLUS' ENTERED AT 09:31:48 ON 18 AUG 2002
S L1

L3 FILE 'REGISTRY' ENTERED AT 09:32:03 ON 18 AUG 2002
1 S L1

L4 FILE 'CAPLUS' ENTERED AT 09:32:04 ON 18 AUG 2002
1 S L3

L5 FILE 'REGISTRY' ENTERED AT 09:32:24 ON 18 AUG 2002
8 S L1 SSS FULL

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FILE 'CAPLUS' ENTERED AT 09:32:38 ON 18 AUG 2002

L6 1 S L5

FILE 'REGISTRY' ENTERED AT 09:34:19 ON 18 AUG 2002

L7 STRUCTURE UPLOADED

L8 0 S L7

L9 0 S L7 SSS FULL

L10 STRUCTURE UPLOADED

L11 6 S L10

L12 136 S L10 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:37:05 ON 18 AUG 2002

=> s 12

L13 1150557 12

=> d ibib abs hitstr l13 1-20

L13 ANSWER 1 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618739 CAPLUS

TITLE: One-pot synthetic method of carbonothiolates:
Selenium-catalyzed reaction of alcohol, disulfide and carbon monoxide

AUTHOR(S): Yutaka, Nishiyama; Takeshi, Maehira; Junko, Nakase; Noboru, Sonoda

CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, 564-8680, Japan

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-346. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB The development of a convenient and efficient method for the synthesis of S-aryl and S-alkylcarbonothiolates has attracted considerable attention in org. synthesis. In this presentation* we will describe a one-pot synthetic method of carbonothiolates by the reaction of alc., disulfide and carbon monoxide in the presence of a catalytic amt. of selenium. When ethanol was allowed to react with di-Ph disulfide in the presence of a catalytic amt. of selenium (0.1equiv.) and an excess amt. of triethylamine as a base in THF solvent under the pressure of carbon monoxide (25 atm) at 25 *-C for 6 h, S-phenyl-O-ethylcarbonothiolate was obtained in almost quant. yield. For ethanol, butanol and benzylalc., the corresponding S-phenyl-O-alkylcarbonothiolates were obtained in 100, 93, and 77 % yields, resp. In the case of secondary alc. like iso-propanol, the reaction was not completed under the same reaction conditions as that of primary alc. giving S-phenyl-O-i-propylcarbonothiolate in only 12 % yield. The yield of coupling product was improved by the reaction under harder reaction conditions *iCO (70 atm) at 80 *-C for 13 h*j. Similarly*Cethanol was reacted with various diaryl disulfides to give the corresponding S-aryl-O-methylcarbonothiolates in excellent to good yields. One-pot synthesis of S-alkyl-O-alkylcarbonothiolate by the selenium-catalyzed coupling reaction of alc., dialkyl disulfide and carbon monoxide was nextly examd. In the use of triethylamine as a tertiary amine, the yields of S-alkyl-O-alkylcarbonothiolates were very low; however, the yields were improved by the use of DBU was used as a base, S-alkyl-O-alkylcarbonothiolates were synthesized in moderate yields. In summary, selenium-catalyzed one-pot synthetic method of carbonothiolates

by the reaction of alc., disulfide and carbon has been developed.

L13 ANSWER 2 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618670 CAPLUS
TITLE: Pyrolysis of phenyl benzoate
AUTHOR(S): Kidder, Michelle K.; Britt, Phillip F.; Buchanan, A. C., III
CORPORATE SOURCE: Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37831, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-276. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The thermal degrdn. of diaryl esters currently is of interest. However, the low temp. pyrolysis of diaryl esters has not been studied in great detail. Here the pyrolysis of Ph benzoate was studied neat and dild. in naphthalene at 400 .degree.C. The major products from the pyrolysis of the neat substrate were benzene, phenol, and benzoic acid, while smaller amts. of biphenyl, benzophenone, Ph biphenylcarboxylate, and Ph benzoylbenzoate were obsd. Surprisingly, the reaction rate increased ca. 30% when Ph benzoate was dild. 10-fold in naphthalene and 1- and 2-phenylnaphthalene (12.8 +/- 2.1 mol%) were formed at the expense of Ph biphenylcarboxylate. Although C-O homolysis (bond dissocn. energy=70 kcal/mol), should not occur to an appreciable extent at 400 .degree.C, these products indicate that Ph radicals are produced in the reaction. Ph radicals could be produced from the decompn. of benzoic anhydride, formed from the condensation of benzoic acids, but the addn. of water (10-20 mol%) reduced the formation of Ph biphenylcarboxylate ca. 40-58%. The mechanistic origins of the products will be discussed in the presentation.

L13 ANSWER 3 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618658 CAPLUS
TITLE: Advances in the asymmetric construction of architecturally complex natural products: The lituarines
AUTHOR(S): Smith, Amos B., III; Frohn, Michael; Walsh, Shawn P.
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-264. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The lituarines A, B, and C comprise a small class of highly complex, bioactive natural products isolated from the sea pen *Lituarina australasiae*. Recently we initiated efforts to develop a convergent, stereocontrolled synthesis of these novel macrolides. Early achievements include an efficient construction of (+)-2 via the 6-endo cyclization of an epoxy-alc. to access the C(8-12) tetrahydropyran ring and a kinetically controlled acid-catalyzed spiroketalization. Construction of (-)-3 via common precursor (-)-1 has also been achieved. A summary of these results, as well as addnl. progress will be presented.

L13 ANSWER 4 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

Golam Shameem

ACCESSION NUMBER: 2002:618624 CAPLUS
TITLE: Mechanistic investigation of the olefin cyclopropanation reaction using (Salen)Ru(carbene) catalysts
AUTHOR(S): Jing, Huanwang; Nguyen, SonBinh T.
CORPORATE SOURCE: Department of Chemistry, Northwestern University, Evanston, IL, 60208-3113, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-230. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The cyclopropanation of styrene by several diazo-compds. R1R2CN2 (R1=H, R2=CO2Et (1, EDA); R1=H, R2=CO2tBu (2, tBDA); R1=H, R2=SiMe3 (3); R1=R2=phenyl (4); R1=H, R2=H (5); R1=H, R2=phenyl (6); and R1=CH3CO, R2=CO2Et (7)) using (Salen)Ru(PPh3)2 as catalyst (salen=1,2-ethanediamino-N,N'-bis(3,5-di-tert-butyl-salicylidene) (A); (S,S)-(+)-1,2-cyclohexanediamino-N,N'-bis(3,5-di-tert-butyl-salicylidene) (B, made in-situ); and 1,2-ethanediamino-N,N'-bis(salicylidene) (C)) were investigated. Although the formation of metal carbene complexes can be obsd. at room temp. for all reactions, the catalytic cyclopropanation of styrene occur only when EDA or tBDA is present. The reaction intermediates and metal carbene complexes were monitored by UV and 1H NMR spectroscopy. Interestingly, the stoichiometric reaction between carbene complexes and styrene do not lead to cyclopropane product. Reaction results between deuterated ethyldiazoacetate and styrene in the presence of a pre-formed ruthenium ethyldiazoacetate carbene complex only gave deuterated cyclopropane. These results suggested that the mechanism of cyclopropanation for our ruthenium salen system do not make use of either a carbene-transfer process or a bis-carbene transfer mechanism. Rather, the diazo-compd. coordinated carbene complex [(Salen)(R1R2N2)Ru=CR1R2] is proposed as an intermediate. The carbene complexes ((Salen)Ru=CHSiMe3) (3) and ((Salen)Ru=CPh2) (4) were prepd. and characterized by 1H and 13C NMR spectroscopy, FAB-MS, and elemental anal. The structure of carbene 4 was detd. by X-ray crystallog. Complex 4 crystallizes in triclinic cell with dimensions: a=11.409(2) .ANG., b=12.308(2) .ANG., c=16.032(3) .ANG., .alpha.=68.968(2).degree. , .beta.=85.531(3).degree. , .gamma.=70.416(2).degree. , V=1977.4(5) .ANG.3, space group: P-1, Z=2, .rho. calcd=1.27 g/cm3.

L13 ANSWER 5 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618614 CAPLUS
TITLE: Chelation-assisted C-H activation and its application in hydroesterification of unsaturated compounds and in doubly catalytic cross-coupling reactions
AUTHOR(S): Chang, Sukbok; Ko, Sangwon; Na, Youngim; Han, Soobong; Kang, Byungman
CORPORATE SOURCE: Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, S. Korea
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-220. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB An efficient and catalytic protocol of hydroesterification of unsatd.

comps. has been developed without a need of CO atm. With the introduction of 2-pyridyl moiety as a chelating group in formate, Ru₃(CO)₁₂ catalyzed activation of formyl C-H bond of formate and subsequent addn. of the intermediate to alkenes and alkynes proceeds with almost complete suppression of decarbonylation. Stereoselectivity of the produced one carbon elongated esters was good to excellent for the formation of linear adduct depending on the bulkiness of the alkenes used. This procedure could be readily applied to a variety of olefins such as terminal, internal, cyclic, bicyclic, vinyl ether, and conjugated enone systems with high efficiency and selectivity. It could be also applied to hydroesterification of alkynes under the similar conditions. In addns., it was amenable to a solvent free condition with same efficiency. Based on the chelation driven C-H bond activation of formate, a putative mechanism of the Ru-catalyzed hydroesterification of 2-pyridylmethyl formate has been proposed. This method of Ru-catalyzed C-H activation could be combined with Pd-catalyzed cross-coupling reactions, in which aryl iodides were readily reacted with formates to give benzoates in high yields. This represents the first example of transition metal catalyzed transmetallation which could be potentially applied to a variety of coupling reactions.

L13 ANSWER 6 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618601 CAPLUS
TITLE: Hinged molecular capsules
AUTHOR(S): Tunstad, Linda M.; Castro, Peter P.; Kang, Sang-Woo; Nunez, Jose; Zhao, Gang
CORPORATE SOURCE: Department of Chemistry and Biochemistry, California State University Los Angeles, Los Angeles, CA, 90032, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-207. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The synthesis, characterization, and conformational changes (based on VT 1H NMR) of two new bis-cavitand hosts based on resorcinarene macrocycles are reported. The nonconvergent bis-cavitand host "Z", possesses two different concave binding surfaces. The convergent bis-cavitand host "C" takes the shape of a capsule. According to CPK models this capsule possesses a cavity of 12-14 angstroms in length and 6-8 angstroms in width. The hosts are conformationally flexible, as evident by dynamic 1H NMR. Of particular interest to us is capsule "C", which has the potential to open and close (depending on temp.) to bind or release a guest in soln. The flexibility seems to be temp. as well as solvent dependent.

L13 ANSWER 7 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618559 CAPLUS
TITLE: Solid-phase synthesis of 2-aminobenzimidazoles via a polymer bound o-phenylenediamine intermediate
AUTHOR(S): Arvanitis, Elena A.; Player, Mark R.
CORPORATE SOURCE: Chemistry, 3-Dimensional Pharmaceuticals, Cranbury, NJ, 08512, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-164. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The synthesis of a 2-aminobenzimidazole library using Irori Microkans is described. Three points of diversity were introduced in the 2-aminobenzimidazole scaffold, 3. Reductive amination of the com. available 4-formyl-3,5-dimethoxypolystyrene resin, 1 followed by attachment of 4-fluoro-2-nitrobenzoic acid led to the polymer-bound o-phenylenediamine intermediate, 2 after arom. nucleophilic substitution of fluorine with primary amines or anilines and subsequent nitro-redn. Treatment with aryl or aroyl isothiocyanates in the presence of diisopropylcarbodiimide afforded the desired 2-aminobenzimidazoles 3, after cleavage from the support with 10% trifluoroacetic acid. This methodol. was utilized for the synthesis of a 12,000-member library.

L13 ANSWER 8 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618490 CAPLUS
TITLE: Synthesis and secondary structure of .beta.-peptides containing (3R)-amino-D-proline: Expansion of the monomer pool for .beta.-peptide library construction
AUTHOR(S): Porter, Emilie A.; Wang, Xifang; Schmitt, Margaret A.; Weisblum, Bernard; Gellman, Samuel H.
CORPORATE SOURCE: Dept. of Chemistry, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-095. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB A synthesis to a new cationic .beta.-amino acid, (3R)-amino-D-proline (AP), was developed. .beta.-Peptides contg. AP were synthesized via solid-phase peptide synthesis and analyzed for helix formation. 2D-NMR and CD data suggest that these peptides display 12-helical secondary structure in methanol and water. In addn., a 17-residue .beta.-peptide contg. AP shows antibiotic activity. The design of new structure-inducing .beta.-amino acids is important, because a large monomer pool is desirable for the development of .beta.-peptide combinatorial libraries.

L13 ANSWER 9 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618393 CAPLUS
TITLE: Real-time elemental analysis of glass batch mixture by laser induced breakdown spectroscopy
AUTHOR(S): Lal, Bansi; Yueh, Fang-Yu; Singh, Jagdish P.; Ramsey, William G.
CORPORATE SOURCE: Diagnostic Instrumentation & Analysis Laboratory, Mississippi State University, Starkville, MS, 39759, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), NUCL-081. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Transmission, index of refraction, thermal consts., mechanical and chem. characteristics of glass are sensitive to the concn. of its constituents. A real-time direct monitoring of the constituent concn. of the mixt. used to manuf. glass can help in energy conservation besides redn. in the

wastage of raw constituents. Laser-induced breakdown spectroscopy (LIBS) technique is fast emerging as one of the best real-time diagnostic tool for elemental anal. primarily because of its short response time-results are available faster. In this study a glass batch mixt. consisting of SiO₂, Al₂O₃, Na₂CO₃ and CaCO₃ has been chosen for investigation. This mixt. is used to make window glass that has typical compn. of 71%SiO₂, 1%Al₂O₃, 12%Na₂O and 16%CaO. 532nm radiation from a frequency doubled pulsed Nd:YAG laser (Continuum Surelite I) is focused on the sample using a 500mm focal length, UV grade fused silica plano-convex lens which also collects emission from the laser induced spark produced at the focus. The emission from the spark is fed to a spectrometer (24001/mm grating, Spex 500M) through an optical fiber. The spectrometer is fitted with a gated 1024-element intensified diode array detector (Princeton Applied Research Model IDAD-1024). EG&G OMAVISION PC software is used for data acquisition and anal. The optimization of various parameters to get reproducible LIBS data is discussed in the paper.

L13 ANSWER 10 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618354 CAPLUS
TITLE: New results concerning heavy element synthesis
AUTHOR(S): Loveland, Walter D.; Gregorich, Ken; Ginter, T. N.;
Ninov, V.; Patin, J. B.; Peterson, D.; Collaboration,
SHEIKS
CORPORATE SOURCE: Department of Chemistry, Oregon State University,
Corvallis, OR, 97331, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting,
Boston, MA, United States, August 18-22, 2002 (2002),
NUCL-042. American Chemical Society: Washington, D.
C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB We report the confirmation of the synthesis of element 110 using the
208Pb(64Ni,n) reaction. Two events, consisting of an implanted heavy atom,
followed by the emission of alpha-particles, were obsd. The cross section
was 5.5 (+7.3, -2.4) pb. We report upper limit cross sections (1 event)
for the prodn. of element 118 in the 208Pb(86Kr,n) reaction of 0.6 and 0.4
pb for EVR magnetic rigidities of 2.00 and 2.12 Tm. Reanal. of
the primary data files from the previous 1999 expt. showed the previously
reported element 118 events are not in the original data. We report an
upper limit (1 event) for the prodn. of element 112 in the 238U(48Ca,3n)
reaction of .apprch. 1 pb. Measurements of .GAMMA.n/.GAMMA.f for excited
No and Hs nuclei are reported. These measurements were made (a) counting
the emitted neutrons in these reactions and (b) by measuring the fusion
and EVR cross sections.

L13 ANSWER 11 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618337 CAPLUS
TITLE: Teaching nuclear and radiochemistry laboratory at
Washington University
AUTHOR(S): Sarantities, D. G.
CORPORATE SOURCE: Department of Chemistry, Washington University, St.
Louis, MO, 63130, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting,
Boston, MA, United States, August 18-22, 2002 (2002),
NUCL-025. American Chemical Society: Washington, D.
C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

Golam Shameem

AB Over the past 30 yr, an extensive list of expts. has been developed that include a broad variety of radiochem. methods and nuclear instrumentation. In a one semester course chem. students perform 12 out of 17 well-structured expts. A list of five addnl. more advanced expts. is also offered to the physics students as part of their measurements lab. The contents and methods of teaching these expts. will be described.

L13 ANSWER 12 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618295 CAPLUS

TITLE: Optically detected magnetic resonance studies of .pi.-conjugated materials

AUTHOR(S): Shinar, J.; Li, G.; Jabbour, G. E.

CORPORATE SOURCE: Department of Physics and Ames Lab, Iowa State University, Ames, IA, 50011, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MTLS-014. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB The electroluminescence- and elec.-detected magnetic resonance (ELDMR and EDMR, resp.) of 2,3,7,8,12,13,17,18-octaethylporphine Pt (PtOEP)-based electrophosphorescent OLEDs is described. At room temp. the measurements yield a neg. (EL-quenching) spin 1/2 resonance similar to those exhibited by fluorescence-based OLEDs. This resonance was concluded to result from magnetic resonance enhancement of the formation of neg. bipolarons at the org.-cathode interface, which enhances the nonradiative quenching of singlet excitons (SEs). It is therefore suspected that similar quenching of SEs by charges at the org./cathode interface may compete significantly with the transfer of the SE energy to TEs in the electrophosphorescent devices as well.

L13 ANSWER 13 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618139 CAPLUS

TITLE: Potent noncovalent thrombin inhibitors featuring P3-heterocycles with P1-aminobenzisoxazole arginine surrogates

AUTHOR(S): Semple, J. Edward; Araldi, Gian Luca; Cui, Jingrong Jean; Kemp, Scott; Komandla, Mallareddy; Siev, Daniel V.; Mamedova, Lala; Reiner, John E.; Gibson, Tony S.; Gaudette, John A.; Minami, Nathaniel; Lawrence, C. Maxwell; Anderson, Susanne M.; Bradbury, Annette E.; Nolan, Thomas G.

CORPORATE SOURCE: Department of Medicinal Chemistry, Corvas International, Inc, San Diego, CA, 92121, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-288. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Thrombin (FIIa), a multifunctional serine protease with trypsin-like specificity, plays a central role in the blood coagulation cascade by mediating the conversion of fibrinogen to fibrin and by activation of platelets. The high incidence of heart attack and cardiovascular disease resulting from up-regulation of thrombin represents a leading cause of morbidity and mortality in the industrialized world. Because of this role and other key biol. functions it facilitates in aberrant thrombosis and

hemostasis, thrombin has attracted much attention as a therapeutic target in the pharmaceutical industry. Our quest for potent, selective, non-covalent FIIa inhibitor scaffolds with improved efficacy and oral bioavailability profiles (Bioorg. Med. Chem. Lett. 2002, 12, 743; *ibid.* In press) led us to pursue novel classes of P1-heterobicyclic arginine surrogates. The design, synthesis and biol. activity of inhibitors 1 that feature the P1-aminobenzisoxazole residue will be presented.

L13 ANSWER 14 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618059 CAPLUS
TITLE: Development of selective CXCR4 inhibitors with strong anti-HIV activity
AUTHOR(S): Tamamura, Hirokazu; Hiramatsu, Kenichi; Omagari, Akane; Oishi, Shinya; Nakashima, Hideki; Peiper, Stephen C.; Otaka, Akira; Fujii, Nobutaka
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyoto University, kyoto 606-8501, Japan
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-207. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB We have discovered a highly selective CXCR4 antagonist, T22 ([Tyr5, 12, Lys7]-polyphemusin II), and its shortened potent analogs, T140 and TC14012, which strongly inhibit the T-cell line-tropic HIV-1 (X4-HIV-1) infection through their specific binding to a chemokine receptor, CXCR4. CXCR4 is the major co-receptor (second receptor) for the entry of X4-HIV-1 into T-cells. It was found to be difficult to generate a T140-resistant strain in vitro as compared to the generation of an HIV strain resistant to other antagonists. Addnl., bifunctional anti-HIV agents based on the specific CXCR4 antagonists (T140 analogs)-3'-azido-3'-deoxythymidine (AZT) conjugation have been synthesized and evaluated, since T140 analogs can possibly work as a carrier of AZT targeting T-cells due to their specific affinity for CXCR4 on T-cells.

L13 ANSWER 15 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:617926 CAPLUS
TITLE: A Series of Macrocyclic ligands: Synthesis and antitumor activity evaluation in vitro
AUTHOR(S): Kong, Deyuan; Martell, Arthur E.
CORPORATE SOURCE: Department of Chemistry, Texas A&M University, College Station, TX, 77842-30012, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-072. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB A series of aza, oxo, and thia- macrocyclic compds. have been synthesized via 2+2 and 3+2 template reaction using divalent lead ions. Preliminary results show that compd. II (3,6,10,18,22,25-hexaaza-31,32-dihydroxy-14,29-dimethyltricyclo[25,3,1,111,17]dotriaconta -1(30), 12, 14,16(32),27,28-hexaene) has antitumor activities against p388, A549 and Hepa 1-6 tumor cell lines; also it can hydrolyze the supercoiled pBR 322 DNA in vitro.

L13 ANSWER 16 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:617907 CAPLUS
TITLE: Large scale preparation of 5,12
-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-trione
AUTHOR(S): Tririya, Gasirat; Zanger, Murray
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University
of the Sciences in Philadelphia, Philadelphia, PA,
19104, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting,
Boston, MA, United States, August 18-22, 2002 (2002),
MEDI-053. American Chemical Society: Washington, D.
C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Doxorubicin and daunomycin are structurally related to the group of
glycoside antibiotics called anthracyclines which show a very high
activity against wide variety of human cancers. Presently, this important
antineoplastic agents has been obtained only by microbial fermn. They
cannot be produced economically by known synthetic methods; thus, the cost
of the drugs is extremely high. These factors have prompted a great
interested in development of synthetic routes to these compds. In general
the synthesis of these agents is divided into three parts: the synthesis
of tetracyclic ring system (aglycon), the synthesis of the aminosugar
moiety, and finally the coupling of the two fragments. The main interest
has been focus on the synthesis of aglycon. In the search for superior
analogs, it was found that the 4-demethoxy analogs of daunomycin and
doxorubicin possess increased activity and decreased toxicity. Thus, it
is considered appropriate to conc. on the synthesis of precursors such as
those leading to the 4-demethoxy aglycon by a simple route and from easily
available starting materials. In this research, the precursor of interest
is 5,12-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-trione.
Currently, two practical and efficient approaches for large scale prepn.
of the precursor have been developed: 1. Diels-Alder reaction of
1,4-benzoquinone with 1,3-butadiene, followed by aromatization using
acetic acid and dimethylation using di-Me sulfate to give
5,8-dimethoxy-1,4-dihydronaphthalene, which is subsequently epoxidized by
using m-CPBA. Epoxide cleavage by Lewis acids such as MgBr₂ etherate is
used to construct 5,8-dimethoxy-2-tetralone. 2. Diels-Alder reaction of
1,4-benzoquinone with 2-chloro-1,3-butadiene, followed by aromatization
and dimethylation to give 2-chloro-5,8-dimethoxy-1,4-dihydronaphthalene,
which is subsequently hydrolyzed by concd. H₂SO₄ to yield
5,8-dimethoxy-2-tetralone. Since 5,8-dimethoxy-2-tetralone can be prepd.
in large quantities, large scale prepn. of the precursor is achieved via
Friedel-Crafts reaction of 5,8-dimethoxy-2-tetralone and phthalic
anhydride. It is hoped that these syntheses will prove to be a practical
approach for prepg. large quantities of the aglycon which will be a useful
precursor for further research involving the synthesis of anthracycline
antibiotics and development of their analogs with increased activity and
decreased toxicity.

L13 ANSWER 17 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:617813 CAPLUS
TITLE: Novel catalytic reaction of hydrogen as a potential
new energy source
AUTHOR(S): Mills, Randell L.; Ray, Paresh; Dong, Jinqun; He,
Jiliang; Chen, Xuemin; Dhandapani, Bala; Good,
William; Voigt, Andreas; Hicks, Steve; Nansteel, Mark;
Dayalan, Ethirajulu; Mayo, Robert
CORPORATE SOURCE: BlackLight Power Inc, Cranbury, NJ, 08512, USA

Golam Shameem

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), INOR-661. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Extreme UV spectroscopy was recorded on microwave discharges of helium with 2% hydrogen. Novel emission lines were obsd. with energies of $q \cdot 13.6$ eV where $q=1,2,3,4,6,7,8,9,11,12$. These lines can be explained as fractional Rydberg states of at. hydrogen formed by the reaction of at. hydrogen with certain catalysts such as He⁺ which ionize at integer multiples of the potential energy of at. hydrogen, 27.2 eV. Fractional-Rydberg-state mol. and mol. ion lines were also recorded. Using alkali catalysts, an inverted Lyman series and the corresponding hydride ions were identified spectroscopically. Novel hydride products were characterized by NMR, ToF-SIMS and XPS. The av. hydrogen atom temp. was 180-210 eV vs. ≈ 3 eV for pure hydrogen. Similarly, Te for helium-hydrogen was 28,000 K compared to 6800 K for pure helium. With a microwave input power of 40 W, the thermal output power was measured to be at least 400 W corresponding to a power d. of 40 MW/m³ and an energy balance of at least -5×10^5 kJ/moleH₂ compared to the enthalpy of combustion of hydrogen of -241.8 kJ/moleH₂. Direct plasmadynamic conversion to electricity was demonstrated.

L13 ANSWER 18 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:617800 CAPLUS
TITLE: Metal-ligand multiple bonds in later, first row complexes
AUTHOR(S): Dai, Xuliang; Kogut, Elzbieta; Wiencko, Heather L.; Zhang, Libei; Warren, Timothy H.
CORPORATE SOURCE: Department of Chemistry, Georgetown University, Washington, DC, 20057-1227, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), INOR-648. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB The later first row metals are extensively used in coordination complexes that catalyze epoxidn. and aziridination. Proposed key steps in this family of catalytic reactions involve the formal transfer of oxo and imido (nitrene) groups to an olefin via metal-ligand multiply-bound species. To synthetically address these intermediates we have prepd. a family of neutral, monovalent complexes [NN]M-L (M=Co, Ni, Cu) supported by a bidentate, monoanionic NN donor ligand. These readily isolable species serve as synthons to highly reactive, 12 to 14-electron two-coordinate metal fragments {[NN]M or [M]} upon dissocn. of a labile ligand L. Exposure to dioxygen leads to trivalent [M]2(μ -O)₂ species that may be isolated or that further react to give the divalent [M]2(μ -OH)₂. Treatment with organoazides leads to either four-coordinate bridged imido complexes [M]2(μ -NR)₂ or unique, three-coordinate terminal imido species [M]=NR. We will present reactivity studies with unsatd. substrates and discuss the role of bridged-terminal equil.

L13 ANSWER 19 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:617757 CAPLUS
TITLE: Anionic water-soluble .beta.-octafluorinated

porphyrins
 AUTHOR(S): Biffinger, Justin C.; Sun, Haoran; DiMagno, Stephen G.
 CORPORATE SOURCE: Department of Chemistry, University of Nebraska,
 Lincoln, NE, 68588-0304, USA
 SOURCE: Abstracts of Papers, 224th ACS National Meeting,
 Boston, MA, United States, August 18-22, 2002 (2002),
 INOR-605. American Chemical Society: Washington, D.
 C.
 CODEN: 69CZPZ
 DOCUMENT TYPE: Conference; Meeting Abstract
 LANGUAGE: English
 AB The first sulfonated water-sol. .beta.-fluorinated porphyrins
 [5,10,15,20-tetrakis-(4-sulfonatophenyl)-2,3,7,8,12
 ,13,17,18-octafluoroporphyrin (1) and 5,10,15,20-tetrakis-(2,6-difluoro-3-
 sulfonatophenyl)-2,3,7,8,12,13,17,18-octafluoroporphyrin(2)]
 have been prepd. The free-base porphyrin is the major species between pH
 3-11 for (1) and between pH 0-9 for (2). Various transition metals were
 successfully inserted [Zn(II), Co(II), Mn(III), Fe(III), Rh(III)]. The
 rhodium porphyrins of (1) and (2) were alkylated in water from the
 rhodium(I) compd. and iodomethane. Co(II) and Mn(III) oxidn. chem. in
 aerobic and anaerobic solns. will also be discussed along with their
 electrochem. behavior.

L13 ANSWER 20 OF 1150557 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2002:617723 CAPLUS
 TITLE: Unusual chemistry of dodecaalkoxy-closo-dodecaborate(-
 2)ions
 AUTHOR(S): Hawthorne, M. Frederick; Huertas, Ramon; Peymann,
 Toralf; Knobler, Carolyn B.
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, University
 of California, Los Angeles, Los Angeles, CA, 90095,
 USA
 SOURCE: Abstracts of Papers, 224th ACS National Meeting,
 Boston, MA, United States, August 18-22, 2002 (2002),
 INOR-571. American Chemical Society: Washington, D.
 C.
 CODEN: 69CZPZ
 DOCUMENT TYPE: Conference; Meeting Abstract
 LANGUAGE: English
 AB Perhydroxylation of [closo-B12H12]2- produces the [closo-B12(OH)12
]2-, 1, which serves as a precursor for carboxylate ester and alkoxyl
 closomers, [closo-B12(OCOR)12]2-and [closo-B12(OCH2R)12
]2-, 2, resp. The alkoxyl derivs. are produced by the reaction of an
 alkyl halide with 1 in the presence of diethylisopropyl amine. The one-
 and two-electron oxidn. of 26-electron 2 produces the corresponding
 25-electron radical anion, 3, and the 24-electron neutral species, 4,
 resp. A variety of alkoxyl derivs. have been investigated and their
 electrochem. behavior correlated with their structures. Back-bonding of
 the nonbonded electrons present on the alkoxyl oxygen atoms with the
 electron deficient hypercloso borane cage stabilizes 3 and 4. The
 structure of the stable electron deficient 4species displays a Jahn-Teller
 distortion to D3d symmetry. The reactions, structures and bonding of
 these novel closomer species will be.

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Date of mailing (day/month/year) 07 March 2001 (07.03.01)	
International application No. PCT/US00/16319	Applicant's or agent's file reference X-12420
International filing date (day/month/year) 11 July 2000 (11.07.00)	Priority date (day/month/year) 19 July 1999 (19.07.99)
Applicant LIN, Ho-Shen et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
24 January 2001 (24.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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